US EPA ARCHIVE DOCUMENT

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 13

05/13/91

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Sulfosate (trimethylsulfonium carboxymethylamino-methylphosphonate; formerly SC-0224): Company Response.

Project No.: 0-1997
EPA Nos.: 9F03796
MRID No.: 416330-01
Tox. Chem. No.: 893C
Submission No.: S383655
DP BAR CODE: D156532

TO: R.Taylor/C.Giles, PM Team # 25
Registration Division (H7505C)

FROM: Nguyen B. Thoa, Ph.D.
Section I, Toxicology Branch I
Health Effects Division (H7509C) 4/12/91

THRU: Roger L. Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (H7509C) 4/12/91 KB 5/6/91

REGISTRANT: ICI Agricultural Products, Wilmington, Delaware.

I. Conclusions:

Technical grade sulfosate ( tech SC-0224) is usually supplied as an aqueous solution containing about 52.2% active ingredient. The very viscous nature of sulfosate precludes the practical manufacture of a technical grade with a standard a.i. content (sulfosate forms an intractable glass-like product if its water content is $\leq$ 30%).

SC-0224 used in the 3-month subchronic oral toxicity study in Beagle dogs (MRID 41209903) is an aqueous solution of the technical product containing 19.2% a.i..

A review of the TOX ONE-LINERS further reveals that several technical sulfosates, each one an aqueous solution with a different a.i. content, were used (1982-present time) in the toxicological studies conducted to support registration of the technical material. These a.i.contents vary from 19.2 to 72%.

II. Action Requested:

Review Addendum to MRID 41209903 (Three months subchronic oral toxicity study with SC-0224 in Beagle dogs) for adequacy of

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a.i. concentration of the technical grade test material used.

III. Background:

TB wished to know why the technical grade SC-0224 used in a 3-month subchronic oral toxicity study in Beagle dogs (MRID 41209903) had only an a.i. content of 19.2% (w/w).

The registrant's explanations are on page 5 of their response, a copy of which is attached. The confidential appendix referred on this page is not attached.



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SUMMARY

The Toxicology Branch has requested an explanation of why MRID# 41209903 "Three Month Subchronic Oral Toxicity Study with SC-0224 in Beagle Dogs", Report No. T-11002 was conducted with lower strength technical (19.2% w/w) than we seek to register for use in corn (Tolerance Petition No.9F3796). In the early stages of development before the optimum sulfosate concentration level was established, a 19.2% aqueous solution of the trimethylsulfonium salt of N-phosphonomethyl glycine (SC-0224) was prepared to support certain toxicology studies. A comparison of composition analysis (see Confidential Appendix, Table 1) for typical technical batches containing 19.1% w/w and 52.2% w/w (EPA Reg. No. 10182-00276), indicates the impurities in the batches are essentially the same with only a change in water content. Thus, the sulfosate product has remained essentially the same over time with the only change being a reduction in water.

Experience has shown that if the water content of SC0224 technical is reduced below 30%, the viscosity of the technical is increased until an intractable glass is formed. In this glass form, SC-0224 technical is extremely difficult to remove from a container and is impractical to formulate. Additionally, reducing the water content of SC-0224 requires heating at relatively high temperatures which decreases the chemical stability. For these reasons, experience has show that the only practical way to supply technical sulfosate is as an aqueous solution, preferably near the 52% concentration.

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008348

MAY 13 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Sulfosate (trimethylsulfonium carboxymethylamino-methylphosphonate, formerly SC-0024): Application for Amended Registration, Petition for Tolerance in or on corn (Petition No. 9F3796) and Toxicological Data Review.

| | | | |
|---|---|---|---|
| Project No.: | 0-0523 | Tox. Chem. No.: | 893C |
| EPA Nos.: | 10182-276 | Record Nos.: | 162448 |
| | 10182-277 | | 162449 |
| | 9F3796 | | 250410 |

TO: R.Taylor/C.Giles, PM Team # 25
Registration Division (H7505C)

FROM: Nguyen B. Thoa, Ph.D. 5/3/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head 5-3-91 6/5/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

I. Actions Requested:

A. Amended Registration and Requested Tolerances

ICI Americas, Inc., Agricultural Products, Wilmington, Delaware, has applied for an amended registration for the products Touchdown Concentrate Herbicide (Technical grade containing 52.2% sulfosate ai; EPA file symbol 10182-ETA) and Touchdown 4LC Herbicide (formulation containing 39.9% sulfosate ai; EPA file symbol 10182-ETT) for use on corn and has also submitted a petition for tolerances for "Touchdown" on corn. The proposed tolerances are for carboxymethylaminomethylphosphonate and its metabolite, AMPA, resulting from the use of the above 2 herbicides on/in field corn.

The proposed residue tolerances are as follows:

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|---|---|
| corn, grain | 0.1 ppm |
| corn, forage | 0.1 ppm. |
| corn, fodder | 0.2 ppm |

These values are similar to tolerance levels values which are already established for the combined residues of glyphosate

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(carboxymethylaminomethylphoshonate), and its metabolite aminomethylphosphonic acid (AMPA) resulting from application of the isopropylamine salt of glyphosate in/on several raw agricultural commodities (40 CFR 180.364).

B. Toxicological Data Review

The following toxicological studies with technical sulfosate were submitted to TB for review:

1. 4-hr acute inhalation toxicity study in the rat (MRID No. 412359-01)

2. 3-month Dietary Toxicity Study with SC-0224 in Rats (MRID No. 412099-02)

3. 3-Month Subchronic Oral Toxicity Study with SC-0224 in Beagle Dogs (MRID No. 412099-03)

4. ICI-0224: Metabolism Study in Rats (MRID No. 412539-03)

5. Supplemental information on a one-year dog feeding study (MRID No. 412359-02) and combined chronic feeding /oncogenicity studies in rats and mice (MRID Nos. 412099-05 AND 412099-07).

II. Conclusions:

A. The Toxicology Data Base is incomplete and cannot support the amended registration and proposed tolerances. The following are data gaps:

1. Acute delayed Neurotoxicity/hen: Sulfosate is a salt composed of a fixed tertiary sulfur cation (trimethyl-sulfonium) and a phosphonate anion (carboxymethyl-aminomethylphosphonate).

2. Acute Neurotoxicity/mammals: this test will be required to support the registration of pesticides in the near future. It is presently required for sulfosate because this compound has demonstrated general neurotoxic symptoms in acute oral, dermal, and inhalation toxicity studies.

3. 90-Day Neurotoxicity/mammals: Sulfosate has demonstrated neurotoxicity in acute oral, dermal and inhalation toxicity studies.

4. Acute Inhalation toxicity study with Touchdown 4LCE.

5. In addition, TB will require a 90-Day Neurotoxicity/hen if the above mentioned acute delayed Neurotoxicity/hen is positive.

B. Toxicological Data Review:

1. Based on the results of the acute inhalation study with technical sulfosate, the actual concentration reached by the test material in the rats' breathing atmosphere was 5.18 mg/L and the $LC_{50}$ is > 5.18 mg/L (4-hr/nose only). A limit test, however, was not considered to have been reached, because the MMAD ± SD of the particles (4.56 ± 2.06 $\mu$) was well above that recommended by EPA for rodents inhalation studies (Memo by S. Gross, dated 04/18/89, entitled "Comments on Standard Evaluation Procedures, Inhalation Testing, SEP/Inhalation"). According to the memo, TB will generally accept an inhalation study with reported MMRDs in excess of the respirable size (1 $\mu$ ) if at least 25% of the particles were $\leq$ 1 $\mu$. Only about 3.9% of the particles in the present study were < 1 $\mu$ and 20% were < 2.5 $\mu$ (inhalable size). The registrant did not explain why an adequate amount of particles of respirable size could not obtain. Systemic effects were observed, including salivation (cholinergic effect) and subdued behavior, splayed gait, head/paw flicking strereotypy, tail erection, and shaking (neurotoxic effects).

   This study is classified as "Supplementary", and can be upgraded to acceptable upon submission of evidence showing that the best efforts were made to generate the experimental aerosol. This study is not a data gap because another acute Inhalation study with technical sulfosate (MRID 249802), classified acceptable, is already available.

2. Based on the results of the 3-month subchronic oral study in rats, the NOELs were 800 ppm (36 mg/kg/day; MDT) in male rats and 2000 ppm (108 mg/kg/day; HDT) in female rats. The LOEL in male rats was 2000 ppm (88 mg/kg/day), based on a significant overall decrease of body weight gain (22% below control). At 2000 ppm, the females exhibited only some decrease in body weight which were significant but minimal and sporadic (6% at week 2, 8% at week 11, & 10% at week 13) and were concommitant with decreases in food consumption (21% at week 2, 18% at week 11, & 7% at week 13).

   This study is classified Acceptable.

3. Based on the results of the 3-month subchronic oral gavage study, the NOEL in male and female Beagle dogs was 10 mg/kg/day (MDT). The LOEL was 50 mg/kg/day (HDT), based on earlier onsets and increase incidences of emesis and salivation. No significant changes were observed in any of the following: body weight, food consumption, urinalysis, organ



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weights, macroscopic/microscopic histopathology, hematology, cholinesterase activity, and clinical chemistry.

This study is classified Acceptable.

4. Based on the results of the metabolism study in rats with $^{14}C$-sulfosate (ICI-0224) radiolabeled on the anion portion of the molecule, the following conclusions were made:

a. Intravenously or orally administered $^{14}C$-sulfosate was rapidly and extensively excreted. Over a 5-day period most (86- 95%) of the dose administered was excreted in the urine and feces. Intravenously treated males and females eliminated 90% of the administered dose in the urine.

b. Absorption of sulfosate was incomplete by the oral route: males and females treated with an oral dose of 25 mg/kg (LD) or with repeated oral LDs, and males treated with a single oral dose of 250 mg/kg (HD) eliminated 47-57% of the administered dose in the urine (absorbed fraction) and 36-42% in the feces (unabsorbed fraction). Females treated with an oral HD eliminated even less in the urine (36% of administered dose) and more in the feces (54% of administered dose). Elimination of $^{14}CO_2$ in the expired air was negligible (result of pilot study).

c. Less than 0.32% of the administered dose remained in the tissues. Less than 2.2% of the administered dose remained in the carcasses (mostly in the bones: 3-7 ppm in LD rats; 19-32 ppm in HD rats).

d. Most of the excreted radioactivity (77-96% of fecal radioactivity content; 80-95% of total urinary radioactivity content) was recovered as unchanged anion (carboxymethylaminomethyl- phosphonate). One fecal metabolite, which accounted for 8.5% of the total fecal radioactivity in repeatedly- dosed females, was tentatively identified as the decarboxilated metabolite aminomethylphosphonic acid (no mass spectral confirmation due to insufficient quantity).Several minor unidentified metabolites were also recovered. Most of these accounted for $\leq$ 3% of the total urinary/fecal radioactivity content.

This study is classified Acceptable.

The Data Evaluation Records (DER) for the above studies are attached along with a review of the supplementary information, and summaries of these studies are included in the updated Toxicity Profile below.

C. The proposed tolerances for Touchdown on corn (section F, vol.12, pp.12, Tolerance petition No: 9F 3796) only included the anionic component of the sulfosate molecule and its

metabolite AMPA but did not include trimethylsulfonium, the cation component. This omission should be addressed.

D. Two formulations, Touchdown 4LC and Touchdown 4LCE are included in the HED tox one-liners. In their application for amended registration for the formulated product, the registrant refers to it as Touchdown 4LC, but the data submitted on its ai content (39.9% ai) and on its acute toxicity (vol 1, pg 12, Petition package) clearly described Touchdown 4LCE. This discrepancy should be corrected because of the big difference in the acute toxicity between 4LC and 4LCE (see attached Toxicological Profile below).



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Toxicological Data Requirements (CFR 158.340)

Technical Sulfosate[a]: (formerly SC-0224)

Use Pattern: New chemical/first food use

Last Updated: 3/05/91

| | | Required | Satisfied |
|---|---|---|---|
| 81-1 | Acute Oral Toxicity | Yes | Yes |
| 81-2 | Acute Dermal Toxicity | Yes | Yes |
| 81-3 | Acute Inhalation Toxicity | Yes | Yes |
| 81-4 | Primary Eye Irritation | Yes | Yes |
| 81-5 | Primary Dermal Irritation | Yes | Yes |
| 81-6 | Dermal Sensitization | Yes | Yes |
| 81-7 | Acute Delayed Neurotox/hen | Yes[b] | No |
| | Acute neurotoxicity/mammals | Yes[c] | No |
| 82-1(a) | 90-Day Oral (rodent) | Yes | Yes |
| 82-1(b) | 90-Day Oral (non-rodent) | Yes | Yes |
| 82-5(a) | 90-Day Neurotoxicity/hen | d | |
| 82-5(b) | 90-Day Neurotoxicity/mammals | Yes[e] | No |
| 83-1(a) | Chronic Toxicity (rodent) | Yes | Yes |
| 83-1(b) | Chronic Toxicity (non-rodent) | Yes | Yes |
| 83-2(a) | Oncogenicity study (rat) | Yes | Yes |
| 83-2(b) | Oncogenicity study (mouse) | Yes | Yes |
| 83-3(a) | Teratology (rat) | Yes | Yes |
| 83-3(b) | Teratology (rabbit) | Yes | Yes |
| 83-4 | 2-generation Reproduction (rat) | Yes | Yes |
| 84-2(a) | Mutagenicity - Gene Mutations | Yes | Yes |
| 84-2(b) | Mutagenicity - Structural Chromosomal Aberrations | Yes | Yes |
| 84-4 | Mutagenicity - Other Genetic Effects | Yes | Yes |
| 85-1 | Metabolism | Yes | Yes |

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a. The various "technical grade sulfosates" used in the toxicological studies described under "Toxicological Profile" are either an aqueous sulfosate concentrate containing 62% ai or aqueous dilutions of this concentrate to ai concentrations of 19.2, 52, and 56.17%.
b. Sulfosate is a salt composed of a fixed tertiary sulfur cation (trimethylsulfonium) and a phosphonate anion (carboxymethylaminomethylphosphonate).
c. Required for all new pesticides in the near future.



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d. The need for this study depends on the results of the acute delayed neurotoxicity/hen study.
e. Neurotoxic signs were observed in acute oral, dermal, and inhalation toxicity studies (see toxicological profile below).

III. Data Requirements (CFR 158.340)

Formulation Touchdown 4LC (41.4% ai):

Use Pattern: New chemical/first food use

Last Updated: 3/05/91

| | | Required | Satisfied |
|---|---|---|---|
| 81-1 | Acute Oral Toxicity | Yes | Yes |
| 81-2 | Acute Dermal Toxicity | Yes | Yes |
| 81-3 | Acute Inhalation Toxicity | Yes | Yes |
| 81-4 | Primary Eye Irritation | Yes | Yes |
| 81-5 | Primary Dermal Irritation | Yes | Yes |
| 81-6 | Dermal Sensitization | Yes | Yes |
| 82-2 | 21-Day Dermal | Yes | No |

Formulation Touchdown 4LCE (39.8% ai):

Use Pattern: New chemical/first food use

Last Updated: 3/05/91

| | | Required | Satisfied |
|---|---|---|---|
| 81-1 | Acute Oral Toxicity | Yes | Yes |
| 81-2 | Acute Dermal Toxicity | Yes | Yes |
| 81-3 | Acute Inhalation Toxicity | Yes | No |
| 81-4 | Primary Eye Irritation | Yes | Yes |
| 81-5 | Primary Dermal Irritation | Yes | Yes |
| 81-6 | Dermal Sensitization | Yes | Yes |
| 82-2 | 21-Day Dermal | Yes | Yes |



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IV. TOXICOLOGICAL PROFILE

Updated 3/05/91

SULFOSATE TECHNICAL:

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| 81-1 | Acute Oral Toxicity in Rats.<br>MRID 249802<br>STAUFFER CHEMICALS<br># T11185<br>November, 1982.<br><br>Acceptable | $LD_{50}$ = 748 mg/kg (males)<br>$LD_{50}$ = 755 mg/kg (females)<br>Doses used: 500, 550, 600, 700, 800, and 900 mg/kg by gavage<br>Signs: mild to severe depression, prostration, tremors, and slow/shallow respiration.<br>Product tested: SC-0224 62% a.i.<br><br>TOXICITY CATEGORY: 3 |
| 81-2 | Acute Dermal Toxicity in Rabbits<br>MRID 249802, 260508<br>Stauffer CHEMICALS<br># T-11185<br>November, 1982.<br><br>Acceptable | $LD_{50}$ > 2000 mg/kg (Both sexes; intact or abraded skin).<br>Doses used: 800 -2200 mg/kg.<br>Signs: Rabbits with abraded skin showed mild to severe depression at all doses levels and mild to moderate erythema. Rabbits with skin intact showed mild depression and mild erythema.<br>Product tested: SC-0224 62% a.i.<br><br>TOXICITY CATEGORY: 3 |
| 81-3 | Acute inhalation toxicity in rats<br>MRID 249802<br>Stauffer Chem No.<br>T-11084<br>November, 1982<br><br>Acceptable | $LC_{50}$ > 6.9 mg/L (both sexes, 4-hr, whole body exposure)<br>Actual chamber concentration: 6.9 mg/L<br>MMAD = 3.5 um at 64 min.<br>2.8 um at 184 min.<br>SIGNS: wet fur, salivation, chromorhinorrhea<br>Product tested: Sulfosate (62% a.i.)<br><br>TOXICITY CATEGORY 3 |

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| 81-3 | Acute inhalation toxicity in rats<br>MRID 412359-01<br>ICI<br>No: CTL/P/2254<br>08/25/88<br><br>Unacceptable | $LC_{50}$> 5.18 mg/L (4-hr, nose only exposure)<br>Actual chamber concentration: 2.65-6.3 mg/L<br>MMAD: 4.56 ± 2.06 um<br>[20% ≤ 2.5 um (inhalable) & 3.9% ≤ 1 um (respirable)]<br>No mortality observed.<br>SIGNS: (CNS & Autonomic) salivation, splayed gait, head & paw flicking, tail erection, shaking,subdue behavior, slow/deep breathing, decrease response to sound. Effects subsided on day 2.<br>A limit test was not reached since only 3.9% of the aerolised sulfosate particles were of respirable size (EPA requires 25%).<br>Product tested: Sulfosate 57.6% a.i. and [redacted]<br>This study may be upgraded to acceptable when evidences are provided to show that optimum technology was used in generating the sulfosate containing aerosol.<br><br>TOXICITY CATEGORY: |
| 81-4 | Primary Eye Irritation in Rabbits<br>MRID 249802<br>STAUFFER CHEMICALS<br># T-11185<br>November, 1982.<br><br>Acceptable | No effect on cornea.<br>Effects on unwashed eyes: mild iritis (1/6 rabbits), and mild conjunctivitis (6/6 rabbits) at 24 hr (Draize score). All effects reversible by day 7.<br>Effects on eyes washed after 20-30 sec. exposure: mild conjunctivitis (3/3 rabbits) lasting 3 days.<br>Dose used: 0.1 ml SC-0224 62% a.i.<br><br>TOXICITY CATEGORY: 3 (based on mild irritation of conjunctiva). |

EXACT PRODUCT INTENDED FOR REGISTRATION IS NOT TESTED

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| 81-5 | Primary Dermal Irritation in Rabbits<br>MRID 249802<br>STAUFFER CHEMICALS<br># T-11185<br>November, 1982.<br><br>Acceptable | 24-hr exposure.<br>Effects at 24 hr: intact and abraded skin showed mild erythema. Mild edema observed in 3/6 rabbits with skin abraded and 1/6 rabbits with skin intact.<br>All dermal effects reversed within 72 hrs.<br>Primary Irritation Score: 0.67.<br>Dose used: 0.5 ml SC-0224 62% a.i.<br><br>TOXICITY CATEGORY: 4 |
| 81-6 | Dermal Sensitization in Guinea Pigs<br>MRID 258398<br>Richmond Tox. Labs.<br># T-11269<br>October 12, 1984.<br><br>Acceptable | SC-0224 Technical (56.3% a.i) is a mild skin sensitizer (Open Epicutaneous Test) |
| 82-1(A) | Subchronic feeding rat<br>MRID 412099-02<br>Stauffer Chem<br>No. T-10888<br>4-3-87<br><br>Acceptable | NOELs: 800 ppm (MDT, 36 mg/kg/day) in males and 2000 ppm (HDT, 108 mg/kg/day) in females.<br>LOEL: 2000 ppm (88 mg/kg/day) in males, based on a significant overall decrease in body weight gain (22% below controls).<br>The HDT only caused sporadic and minimal decreases in body weight in females (secondary to a feed palability - related reduction in feed intake) and no significant overall decrease in B.W. gain.<br>No significant changes were observed in clinical chemistry, hematology, urinalysis, organ weights, or macroscopic/microscopic histopathology.<br>Doses tested: 0, 150, 350, 800, and 2000 ppm.<br>MTD was reached for males only.<br>Product tested: Sulfosate (19.2% a.i., 75.6% water) |



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| 82-1(b) | Subchronic feeding dog<br>MRID 412099-02/03<br>Stauffer Chem<br>No. T-11002<br>4-3-87<br><br>Acceptable | NOEL: 10 mg/kg/day (LDT)<br>LOEL: 50 mg/kg/day (HDT) based on increase incidences and earlier onset of emesis and salivation. No changes in B.W., food consumption, clinical chemistry, hematology, urinalysis, organ weights, or macroscopic/microscopic histopathology were observed.<br>Doses tested: 0, 10, 25, and 50 mg/kg/day by gavage.<br>Dog's Strain: Beagle<br>Product tested: Sulfosate (19.2% a.i., 75.6% water). |
| 83-1a<br>83-2b | Feeding/Oncogenic (2-year) in Mice<br>MRID 402140-06<br>412099-07<br>Stauffer Chem<br>No. T-11813<br>4/3/87<br><br>Guideline | Oncogenic NOEL: >8000 ppm (HDT)<br>Systemic NOEL: 1000 ppm (MDT)<br>Systemic LOEL: 8000 ppm based on decreases in B.W. and feed consumption (both sexes), increases incidences of white matter degeneration in lumbar spinal cord (males only), and increase incidences of duodenal epithelial hyperplasia (females only).<br>Doses used: 0, 100, 1000, and 8000 ppm<br>Mice strain: Charles River<br>Test material: Sulfosate 56.17% a.i. |
| 83-1a<br>83-2a | Feeding/Oncogenic (2-year) in Rats<br>MRID 402140-07<br>412099-05<br>Stauffer Chem<br>No: T-11082<br>4/4/87<br><br>Guideline | Oncogenic NOEL: >1000 ppm (HDT)<br>Systemic NOEL: 100 ppm (LDT)<br>Systemic LOEL: 500 ppm (MDT) based on decreased levels of lactate dehydrogenase in males and females at 6 and 12 months.<br>Effects at 1000 ppm: Decreases in B.W.(both sexes) and increase incidences of chronic laryngeal and nasopharyngeal inflammation (males).<br>Doses used: 0, 100, 500, and 1000 ppm<br>Rats strain: Charles River CrL:CD (SD)BR.<br>Test material: Sulfosate 56.17% a.i. |



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| 83-1(b) | Chronic Feeding (1-year) in Dogs<br>MRID 402140-05<br><br>Stauffer Chem.<br>No: ECH T-11075<br>4/3/87<br><br>Minimum | Systemic NOEL: 10 mg/kg/day (MD)<br>Systemic LOEL: 50 mg/kg/day (HD) based on decreases in LDH.<br>Doses used: 0, 2, 10, and 50 mg/kg/day, by gavage.<br>Selection of above dose range was based on (i) a 28-Day oral gavage study in which 150 mg/kg/day was lethal within 3 days and 75 mg/kg/day produced emesis, and (ii) a 90-Day study in which 50 mg/kg/day produced increase in emesis and salivation.<br>Dog's Strain: Beagle<br>Test material: Sulfosate 56.2% a.i. |
| 83-3(a) | Teratogenicity in Rats<br>MRID 249802<br>Stauffer Environ. Health Cen.<br>No: T-11050<br>November 1982<br><br>Guideline | Terato.NOEL: >333 mg/kg/day (HDT)<br>Fetotoxic NOEL: 100 mg/kg/day (MDT)<br>Fetotoxic LOEL: 333 mg/kg/day based on significant decreases in B.W.<br>Maternal NOEL: 100 mg/kg/day.<br>Maternal LOEL: 333 mg/kg/day based on significant decreases in B.W. and feed intake.<br>Effects at 333 mg/kg/day: Two deaths. Signs were significant increase in incidences of lethargy, salivation, and chromorhinorrhea.<br>Doses used: 0, 30, 100, and 333 mg/kg/day by gavage to S-D rats.<br>Test material: Sulfosate 19.2% a.i. |
| 83-3(b) | Teratogenicity in Rabbits<br>MRID 260966<br>Stauffer Chem.<br>No: T-11052<br>6/21/83<br><br>Guideline | Developmental NOEL: >100 mg/kg/day (HDT). A/D ratio= 10/<100= <0.1.<br>Maternal NOEL: <10 mg/kg/day (LDT) (Significant increase in incidences of diarrhea, head tilt, nasal discharge, wet stains on chin, red urine stain).<br>Effects at 100 mg/kg/day: 38% mortality, 36% spontaneous abortion, significant decrease in feed intake, and in number of live fetuses per litter.<br>Doses used: 0, 10, 40, and 100 mg/kg/day by gavage to Dla;(NZW)SPF rabbits.<br>Test material: Sulfosate 56.2% a.i. |



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| 83-4 | Reproduction (2-gen) in Rats<br>MRID 258398<br>264429<br>Stauffer Chem.<br>No: T-110-51<br>4/19/84<br><br>Guideline | Reproductive NOEL: >2000 ppm (HDT)<br>Systemic NOEL: 150 ppm (LDT)<br>Systemic LOEL: 800 ppm (MDT) based on reduced feed intake and B.W. in pups and parents, reduced absolute thymus weight (P1 M+F), increase platelet count (F2B adults, M+F).<br>Doses used: 0, 150, 800, and 2000 ppm in Crl CD(SD)Br strain.<br>Test material: sulfosate 19.2% a.i. |
| 84-2(a) | Mutagenicity<br>Reverse mut.<br>(Ames Test)<br>in Salmon. Typhi.<br>MRID 249802<br>Stauffer Chem.<br>No:T-10487<br>1/19/82<br><br>Acceptable | Not mutagenic at concentrations of 0.12, 0.37, 1.11, 3.33, and 10 mg/plate without S9, and of 0.56, 1.11, 1.67, 3.33, 5.0, 10, and 15 mg/plate with S9.<br>Tester Bacteria: TA1535, TA1537, TA1538, TA98, and TA100 from Dr. Ames.<br>Pos. controls: Na azide, 9-aminoacridine (9-AA), 2-nitrofluorene (2-NF), and 2-aminoanthracene (2-AA).<br>Test material:sulfosate 90% a.i (estimated purity). |
| 84-2(a) | Mutagenicity<br>Reverse mut.<br>(Ames Test)<br>in Salmon. Typhi.<br>MRID 260966<br>Stauffer Chem.<br>No: T-12660<br>9/25/85<br><br>Acceptable | Not mutagenic at concentrations of 2.5, 5, 10, 20, and 40 ul/plate, with or without S9.<br>Tester Bacteria: TA1535, TA1537, TA 98, and TA100.<br>Pos. controls: Na azide, 9-AA, 2-NF.<br>Cytotoxic Dose: HDT<br>Test material: Sulfosate 55.6% a.i. |
| 84-2(a) | Gene Mutation<br>(SLRL)<br>in Drosophila<br>melanoga<br>MRID 249802<br>Litton Bionetics<br>No: 22169<br>6/13/82<br><br>Acceptable | Not mutagenic at doses of 25 and 50 mg/ml in "Sex linked recessive lethal test".<br>Pos. control: EMS |



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| 84-2(a) | Gene Mutation<br>(Forward Mut.)<br>Mouse Lymphoma<br>MRID 249802<br>Stauffer Chem<br>T-10848<br>2/8/1982<br><br>Acceptable | Not mutagenic without S9.<br>Significant reproducible increase in mutation frequency in presence of S9. Test medium pH not mentioned but was probably in the acid range.<br>Indicator cells: L5178Y ($TK^+/^-$) mouse lymphoma cell line from Dr. Clive, RTP, No.Carolina).<br>Concentrations used: 0.38, 0.75, 1.50, 3, 6, 8, 8.5, 9, and 10 mg/ml in presence of S9, and 0.38, 0.75, 1.5, 3, 6, 7, 8, 9, and 10 mg/ml w/o S9.<br>Cytotoxic concentrations: >7 mg/ml |
| 84-2(a) | Gene Mutation<br>(forward mut.)<br>Mouse Lymphoma<br>MRID 260966<br>Stauffer Chem.<br>No. T-12661<br>12/19/1985<br><br>Acceptable | Introduction of sulfosate in the test incubation medium reduced its pH to an acid range (5.67 -7.07). Under this experimental condition, sulfosate was positively mutagenic both in the presence of S9, at concentrations of 3-5 ul test material/ml, or without S9, at concentrations of 3.5 to 5ul/ml). When the pH of test incubation medium was readjusted to a physiological level of 7.4 (Addendum of 3/20,1987), concentrations from 5 to 10 ul/ml lost their mutagenic effect<br>Indicator cells: L5178Y($TK^+/^-$) mouse lymphoma cell line (Dr. Clive, RTP, No.Carolina).<br>Test material:Sulfosate 55.6% a.i.<br>Cytotoxic concentrations:<br>Unadjusted acidic medium: >5ul/ml pH adjusted medium: >7.75 ul/ml<br>Pos. controls: N-Nitrosodimethyl-amine (DMN) with S9 and Ethyl-methanesulfonate (EMS) wo S9. |
| 84-2(b) | Mutagenicity<br>Cytogenetic<br>Rat bone marrow<br>MRID 249802<br>Stauffer Chem.<br>No: T-10884<br>september 1982<br><br>Acceptable | Test animals: 6-wk old CD-Crl:CoBScd(SD)BR male rats.<br>Not mutagenic ( did not induce any structural chromosome aberrations in rats' bone marrow cells.<br>Doses used: 21, 63, and 188 mg/kg ($LD_{50}$= 565 mg/kg).<br>Test material: sulfosate 58.5% a.i.<br>Pos. control: cyclophosphamide |



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| 84-2(b) | Mutagenicity (Micronucleus assay) Mouse bone marrow MRID 402140-04 412099-08 Stauffer Chem. No: EHC-T-12689 4/23/87<br><br>Acceptable | Test animals: Charles River D-1 str. Not mutagenic (did not induce any increase in the number of PCE containing micronuclei). Doses used: 700, 900, and 1100 mg/kg in males and 400, 600, and 800 mg/kg in females, based on results of a range finding study in which doses >1400 mg/kg killed 3/3 males within 48 hrs and doses >1000 mg/kg killed 2/3 females. |
| 84-2(b) | Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-10875 7/6/1982<br><br>Acceptable | Positive mutagenicity (induces structural chromosomal aberration in CHO cells both in the absence of S9, at the concentration of 4 mg/ml, and in its presence, at concentrations of 10 and 12 mg/ml. Sister chromatid exchange (SCE) was not determined. Concentrations used: 2, 4, and 6 mg/ml w/o S9 and 2, 4, 6, 8, 10, and 12 mg/ml with S9. Test material: Sulfosate 58.5% a.i. |
| 84-2(b) | Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-11019 7/22/82<br><br>Acceptable | Positive mutagenicity (Induces structural chromosomal aberration in CHO cells both in the absence of S9, at concentrations of 6-8 ul/ml, and in its presence, at 1-8 ul/ml. No increase in SCE was observed. Concentrations used: 2, 4, 6, 8, 10, and 12 ul/ml. Test material: Sulfosate 72% a.i. |
| 84-2(b) | Mutagenicity (cytogenetic) in CHO cells MRID 260966 Stauffer Chem. No: EHC T-12663 12/18/1985<br><br>Acceptable | pH of treatment medium was readjusted to 7.4-7.6 prior to testing. Not mutagenic (did not induce any structural chromosome abberrations in CHO cells or any increase in SCE) at concentrations of 4-10 ul/ml, with or w/o S9. Cytotoxic concentrations: None Pos. controls: Mitomycin C and Cyclophosphamide. Test material: sulfosate 55.6% a.i. |

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|---|---|---|
| 84-2(b) | Mutagenicity (cytogenetic) Mouse Lymphoma MRID 260966 Stauffer Chem. No: EHC T-12662 12/19/82<br><br>Acceptable | Indicator cells: L 5178Y ($TK^{+}/^{-}$) mouse lymphoma cell line from Dr. Clive, RTP, No.Carolina). Sulfosate concentrations of 5 ul/ml (w/o S9) and >3 ul/ml (w S9) induced chromosomal aberrations in the mouse lymphoma cells and increased the number of SCEs when the pH of the test medium was not readjusted (5.62-7.07). When the pH was readjusted to 7.4 concentrations from 4-10 ul/ml were not mutagenic. Cytotoxic concentrations: >5 ul/ml at acidic pH, and $\leq$ 10 ul/ml at physiological pH. Pos. controls: Ethyl methane-sulfonate & N-nitrosodimethylamine. Test material: 55.6% a.i. |
| 84-4 | Mutagenicity BALB/3T cells (morphological transformation) MRID 249802 Stauffer Chem. No: T-10849 1/4/82<br><br>Acceptable | Indicator cells: 1-1 subclone of clone A-31 of BALB/3T3 mouse cells from Dr. Kanunaga (NCI). Not mutagenic (did not induce an increase in the number of transformed foci) Concentrations used: 0.313, 0.625, 1.25, 2.5, and 5 mg/ml . Cytotoxic concentrations: >3 mg/ml Test material: sulfosate 90% estimated purity. |

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| 85-1 | Metabolism in Rats<br>MRID 258398<br>Stauffer Chem.<br>PMS-148<br>2/4/85<br><br>Acceptable | Test material: (Methyl $^{14}C$) trimethylsulfonium Carboxymethylaminomethylphosphonate) 96.5% purity, 20 mci/mmol.<br>Identification of the (Methyl $^{14}C$) trimethylsulfonium ion ($^{14}C$-TMS) in urine and fecal extracts done by TLC, GC/MS, autoradiography, and K iodoplatinate spray.<br>After oral administration of 35 mg/kg (LDT) or 350 mg/kg (HDT) test material to S-D rats of both sexes, the $^{14}C$-TMS ion is rapidly and almost completely absorbed from the GI tract and rapidly excreted unmetabolized mostly via the kidney.<br>Urine recovery of $^{14}C$ (expressed as % of administered dose were: 80.8-95% at 24 hr and 91.4-98.5 at 120 hr. Most (95.3-97%) of the total radioactivity was unmetabolized $^{14}C$-TMS ion.<br>Fecal recovery of $^{14}C$ (expressed as % of administered dose were: 0.72-4.03% at 24 hr and 0.95-7.19% at 120 hr. All the radioactivity was unmetabolized $^{14}C$-TMS ion.<br>$^{14}CO_2$ in expired air was negligible.<br>Tissues residues were negligible: 0-0.148 (LD) and 0-10.6 ppm (HD) sulfosate equivalents.<br>The lack of metabolism may be explained by the hydrophilic nature of TMS ion.<br>Acute toxic effects at the HDT: lethargy, ataxia, slow/labored breathing, salivation, occasional tremors. Signs lessened after 24 hrs. |

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| 85-1 | Metabolism in Rats<br>MRID 412359-03<br>ICI Americas Inc.<br>No: T-12906<br>12/20/88<br><br>Acceptable | Test material: Trimethylsulfonium Carboxymethylaminomethylphosphonate $^{14}C$-radiolabeled on the anionic moity (Carboxymethylaminomethyl-phosphonate), 93.2% radiopurity, 9.8 mCi/mmol.<br>Identification of anion by TLC, autoradiograhy, and GC/MS.<br>Males and females S-D rats iv-treated with 25 mg/kg (LDT) test material excreted 90% of the administered dose in urine.<br>After oral administration of the LDT or the HDT (250 mg/kg), the test material was rapidly excreted in urine and feces (70-82% of the total radioactivity administered was excreted within 24 hrs, and 85-94% within 120 hrs).<br>Absorption was incomplete: only 47-57% of total radioactivity was recovered in urine. Fecal excretion was 36-42% of the administered dose.<br>Most of the recovered radioactivity was unmetabolized carboxymethyl-aminomethylphosphonate (80-90% of urine and 77-96% of feces total radioactivity).One fecal metabolite was aminomethylphoshonic acid (8.5% of total fecal radioactivity in female rats dosed repeatedly (14 single daily LD of unlabeled test material followed by a single LD of labeled test material.<br>$^{14}CO_2$ in expired air was negligible.<br>Combined tissue residues were only $\geq$0.32% of administered dose.<br>Carcasses contained 2.25% of the administered dose, most of it located in bones.<br>Acute toxic signs observed with the HD: lethargy, moderate/severe depression, tremors, dehydration, and reduced feed consumption. Signs lasted 72 hours. |



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IV. TOXICOLOGICAL PROFILE

Updated 3/05/91

FORMULATION TOUCHDOWN 4LC (41.4% a.i.):

| | | |
|---|---|---|
| 81-1 | Acute Oral Toxicity in Rats.<br>MRID 249803<br>STAUFFER CHEMICALS<br># T11189<br>November, 1982.<br><br>Acceptable | $LD_{50}$ = 846 mg/kg (males)<br>$LD_{50}$ = 805 mg/kg (females)<br>Doses used: 0, 650, 700, 800, 900, & 1000 mg/kg by gavage in corn oil.<br>Signs: depression, ataxia, prostration, tremors, ptosis, and slow/shallow respiration.<br><br>TOXICITY CATEGORY: 3 |
| 81-2 | Acute Dermal Toxicity in Rabbits<br>MRID 249803<br>Stauffer CHEMICALS<br># T-11189<br>November, 1982.<br><br>Acceptable | $LD_{50}$: 1316 mg/kg (intact skin), & 1061 mg/kg (abraded skin) for both sexes.<br>Doses used: 450 -1200 mg/kg.<br>Signs: Mild to moderate erythema and edema. Salivation, mild to severe depression, prostration, and tremors in some rabbits at all doses levels.<br><br>TOXICITY CATEGORY: 2 |
| 81-3 | Acute inhalation toxicity in rats<br>MRID 258398<br>Stauffer Chem No.<br>T-11870<br>5/9/1984<br><br>Acceptable | $LCs_{50}$ 1.30 mg/L (males)<br>1.56 mg/L (fem)<br>Aerolized test material became foamy and had to be replaced several times during the 4-hr whole body exposure.<br>MMAD: 1.68- 3.10um (stable particle size was achieved).<br>SIGNS: reduced activity, prostration, and dehydration.<br><br>TOXICITY CATEGORY 3 |



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|---|---|---|
| 81-4 | Primary Eye Irritation in Rabbits<br>MRID 249803<br>STAUFFER CHEMICALS<br># T-11189<br>November, 1982.<br><br>Acceptable | Very corrosive.<br>Unwashed eyes: severe corneal opacity, moderate iritis, and conjunctivitis. Effects cleared on day 24 except in 2 rabbits which still showed moderate to severe corneal opacity and mild conjunctivitis. Effects may be due to the i.i. ethoquat?<br>Eyes washed: ( Exposure of 20-30 sec.) Effects were reduced.<br>Dose used: 0.1 ml<br><br>TOXICITY CATEGORY: 1 |
| 81-5 | Primary Dermal Irritation in Rabbits<br>MRID 249803<br>STAUFFER CHEMICALS<br># T-11189<br>November, 1982.<br><br>Acceptable | Moderate dermal irritant<br>Effects observed after 24-hr exposure (intact or abraded skin):<br>Mild to moderate erythema and edema (6/6 rabbits).<br>Mild edema and scars still observed at 72 hrs.<br>PI Score = 2.92 at 24 hrs.<br>Dose used: 0.5 ml<br><br>TOXICITY CATEGORY: 3 |
| 81-6 | Dermal Sensitization in Guinea Pigs<br>MRID 258398<br>Richmond Tox. Labs.<br># T-11420<br>October 12, 1984.<br><br>Acceptable | Mild skin sensitizer |

IV. TOXICOLOGICAL PROFILE

Updated 3/05/91

FORMULATION TOUCHDOWN 4LCE (39.8% a.i.):

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|---|---|---|
| 81-1 | Acute Oral Toxicity in Rats.<br>MRID 408938-02<br>STAUFFER CHEMICALS<br># T12589<br>2/12, 1987.<br><br>Acceptable | $LD_{50}$ = 1760 mg/kg (males)<br>$LD_{50}$ = 1298 mg/kg (females)<br>SIGNS: depression, hypersensitivity to touch and sound.<br>NECROPSY: dark livers, spleens, and/or lungs, and test-like material in GI tract.<br><br>TOXICITY CATEGORY: 3 |
| 81-2 | Acute Dermal Toxicity in Rabbits<br>MRID 408938-02<br>Stauffer CHEMICALS<br># T-12589<br>November, 1987.<br><br>Acceptable | $LD_{50}$> 2000 mg/kg (Both sexes)<br>SIGNS: mild depression and diarrhea.<br><br>TOXICITY CATEGORY: 3 |
| 81-3 | Acute inhalation toxicity in rats<br>MRID 408938-03<br>Stauffer Chem No. T-12983<br>6/22/1987<br><br>Unacceptable | A respirable aerosol could not be generated: the test material was highly viscous and formed excessive foam. Registrant was advised to pursue additional testing. Ways to reduce foaming were suggested (Dilute test material, reduce surfactants) as well as ways to improve particulation (form dense fog and run through a cyclone separator to remove large particles).<br><br>TOXICITY CATEGORY: Not classified |

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| 81-4 | Primary Eye Irritation in Rabbits<br>MRID 408938-02<br>STAUFFER CHEMICALS<br># T-12589<br>2/12/1987.<br><br>Acceptable | Unwashed eyes: Moderate iritis, and mild to moderate conjunctival irritation. Effects cleared by day 7.<br>Eyes washed: ( Exposure of 20-30 sec.) Mild to moderate conjunctival irritation.<br>Dose: 0.1 ml (pH of test material= 5.85).<br><br>TOXICITY CATEGORY: 3 |
| 81-5 | Primary Dermal Irritation in Rabbits<br>MRID 408398-02<br>STAUFFER CHEMICALS<br># T-12589<br>2/12/1987<br><br>Acceptable | Non-irritating (4-hr exposure)<br><br>TOXICITY CATEGORY: 4 |
| 81-6 | Dermal Sensitization in Guinea Pigs<br>MRID 408398-04<br>Stauffer Chem.<br>No.T-12588<br>8/4/1987<br><br>Acceptable | Not a skin sensitizer (Modified Buehler test). |
| 82-2 | 21-Day Dermal in Rats<br>MRID 412099-04<br>Ciba-Geigy Corp.<br>No: CTL/P/2496,<br>LR0535<br>7/7/89<br><br>Acceptable | Doses: 25, 250, 1000 mg/kg/day (6hr/day/21 days) in 0.0021, 0.0027, and 0.0826 ml/100 g B.W.<br>NOEL= 250 mg/kg (MDT)<br>EFFECTS: dermal irritation in HDT males (dermal histology was normal). Slight increase in testes weight at 25 and 1000 mg/kg/day with normal histology.<br>Occasional sciatic nerve fiber degeneration (1 male and 2 fem. out of a total of 10) at 1000 mg/kg/day. |

V. Data Gaps:

A. With Tech. Sulfosate:

(1) Acute delayed Neurotoxicity/hen (81-7): Sulfosate (formerly SC-0224) is a salt composed of a fixed tertiary sulfur cation (trimethylsulfonium) and a phosphonate anion (carboxymethylaminomethyl-phosphonate). Phosphonate containing OPs are known to cause acute delayed neurotoxicity (DS Barrett & al in "A Review of organophosphorus ester-induced delayed neurotoxicity", Vet. Hum. Toxicol., 27, (1), feb. 1987.

(2) Acute Neurotoxicity/mammals: This test will be required to support the registration of pesticides in the near future. It is presently required for sulfosate because this compound has demonstrated general neurotoxic symptoms in acute oral, dermal, and inhalation toxicity studies.

(3) 90-Day Neurotoxicity/mammals (82-5b): Sulfosate has demonstrated neurotoxicity in acute oral, dermal and acute toxicity studies (MRIDs 249802, 260508, 412359-01).

(4) T.B. may also require a 90-Day Neurotoxicity/hen in the future if sulfosate demonstrates acute delayed neurotoxicity.

B. With The Formulation Touchdown 4LCE:

An acute Inhalation toxicity study is required.

VI. Action Taken to Obtain Additional Information or Clarification:

RD has been notified of the Data Gaps cited above.

VII. Established Tolerances:

There are no existing tolerances for the pesticide sulfosate (trimethylsulfonium carboxymethylaminomethylphosphonate, formerly SC-0024). Tolerances are however established for glyphosate (isopropylamine salt of carboxymethylaminomethylphosphonate), a pesticide closely related in chemical structure to sulfosate (40 CFR 180.364).

VIII. Reference Dose (Rfd):

There are no defined Rfd for sulfosate.

IX. Pending Regulatory Actions:

HED is not aware of any pending regulatory action against the registration of this pesticide.

X. Toxicological Issues Pertinent to Granting this Request:

A. There are 2 Touchdown 4LC formulations. The first one, Touchdown 4LC (41.4% ai), due to one of its inert ingredient, [redacted] is highly dermally toxic (TOX CAT 2) and very corrosive to the eyes (TOX CAT 1), causing severe corneal opacity, and moderate iritis and conjunctivitis. The second one, Touchdown 4LCE (39.8% ai), is only moderately orally and dermally toxic (TOX CAT 3), moderately irritating to the eyes with no corneal effect (TOX CAT 3), not irritating to the skin (TOX CAT 4), and not a skin sensitizer. There is no data on its acute inhalation toxicity.

In their application for amended registration for the formulated product, the registrant refers to this product as Touchdown 4LC, but the submitted data on the ai content (39.9% ai) and on the acute testing (vol 1, pg 12, Petition package) clearly related the product to Touchdown 4LCE. This discrepancy should be corrected because of the big difference in the acute toxicity between 4LC and 4LCE.

B. Sulfosate's potential for neurotoxicity is of concern. The following neurotoxic symptoms were observed in acute oral, dermal, or inhalation studies with both the technical product and the formulation:

(1) Ataxia, tremors, mild to severe depression, prostration (oral route, tech. product, MRID 249802) and depression, ataxia, prostration, tremors (oral route, 4LC, MRID 249803) in rats.

(2) Mild to severe depression (dermal route,, tech. sulfosate, MRID 249802 & 260508) and mild to severe depression, prostration, and tremors (dermal route, 4LC, MRID 249803) in rabbits.

(3) Splayed gait, head and paw flicking, shaking, subdued behavior, decrease response to sound (inha. route, tech. sulfosate, MRID 412359-01) and reduced activity, prostration (inha. route, 4LC, MRID 258398) in rats.

C. The following neurohistopatology were also observed in subchronic and chronic/oncogenicity studies:

(1) White matter degeneration of the lumbar spinal cord of



INERT INGREDIENT INFORMATION IS NOT INCLUDED

male mice (oncogenic study, MRID 402140-06 & 412099-07).

(2) Sciatic nerve degeneration (21-Day dermal, 4LCE, MRID 412099-04).

Organophosphorus Compounds are known to cause neurotoxicity. Sulfosate is a organophosphonate. Several pesticides belonging to this group of chemicals are also known to cause acute delayed neurotoxicity in the hen and in humans.

D. In some of the in-vitro mutagenicity tests conducted in 1982, Sulfosate induced a false positive mutagenic effect. These studies included MRID 249802, studies Nos. T-10848 (Forward mutation/Mouse Lymphoma cells), T-10875 (Structural Chromosomal Abberrations/CHO cells) and T-11019 (Structural Chromosomal Abberrations/CHO cells). A common feature of these tests was that the pHs of the test incubation media were acidic (pH 5.67 -7.07) due to the addition of sulfosate. These positive results were no longer observed [see MRID 260966, studies Nos. T-12661 (Forward Mutation/Mouse Lymphoma cells), T-12662 (Structural Chromosomal Abberrations/CHO cells), and T-12663 (Structural Chromosomal Abberrations/Mouse Lymphoma cells)] when the pH was readjusted to a more physiological level (7.4) before the conduct of the mutagenicity test.

E. Composition of Technical Grade Sulfosate

Technical sulfosate is usually supplied as an aqueous solution containing about 52% active ingredinet. The very viscous nature of sulfosate precludes the practical manufacture of a technical grade with a standard a.i. content (sulfosate forms an intractable glass-like product if its water content is ≤ 30%). The various "technical grade sulfosates" used in the toxicological studies described under "Toxicological Profile" above are either an aqueous sulfosate concentrate containing 62% ai or aqueous dilutions of this concentrate to ai concentrations of 19.2, 52, and 56.17%.

XI. Relevant Consideration in setting the tolerance:

Sulfosate tech. is a salt composed of a fixed tertiary sulfur cation (trimethylsulfonium) and a phosphonate anion (carboxymethylaminomethylphosphonate). After oral administration of sulfosate, the cation is well absorbed and is rapidly excreted unmetabolized. The anion is incompletely absorbed, and is excreted mostly unchanged in the urine and feces. Some anion undergo decarboxilation in the GI tract to form AMPA. In its tolerance petition, the registrant did not include the cation in



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the list of residues for which tolerances levels in/corn are proposed. This omission should addressed by the registrant.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION

EPA No.: 68D80056
DYNAMAC No.: 309-C
TASK No.: 3-09C
March 20, 1991

008368

# DATA EVALUATION RECORD

## SULFOSATE

## Acute Inhalation Toxicity Study in Rats

STUDY IDENTIFICATION: Hext, P. M. ICIA 0224: 4-hour acute inhalation toxicity study in the rat. (Unpublished study No. CTL/P/2254 conducted by ICI Central Toxicology Laboratory, Cheshire, United Kingdom, and submitted by ICI Agrochemicals, Surrey, United Kingdom; dated August 25, 1988.) MRID No. 412359-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: [signature]

Date: 3/19/91



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NOT INCLUDED

1. CHEMICAL: Sulfosate.

2. TEST MATERIAL: ICIA-0224 (technical), lot No. not reported, was 57.6% active ingredient [redacted] and was described as a straw-colored, opaque liquid.

3. STUDY/ACTION TYPE: Acute inhalation toxicity study in rats.

4. STUDY IDENTIFICATION: Hext, P. M. ICIA 0224: 4-hour acute inhalation toxicity study in the rat. (Unpublished study No. CTL/P/2254 conducted by ICI Central Toxicology Laboratory, Cheshire, United Kingdom, and submitted by ICI Agrochemicals, Surrey, United Kingdom; dated August 25, 1988.) MRID No. 412359-01.

5. REVIEWED BY:

Patricia Turck, M.S.
Principal Reviewer
Dynamac Corporation

Signature: Patricia Turck
Date: March 20, 1991

Margaret E. Brower, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Margaret Brower
Date: March 20, 1991

6. APPROVED BY:

Nicolas P. Hajjar, Ph.D.
Department Manager
Dynamac Corporation

Signature: William L. McLellan for
Date: March 20, 1991

N.B. Thwa
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EPA Reviewer, Section I
Toxicology Branch I
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Signature: N Thwa
Date: 4/12/91

Roger Gardner, ~~Ph.D.~~
EPA Section Head, Section I
Toxicology Branch I
(H-7509C)

Signature: Roger Gardner
Date: 4/12/91

7. CONCLUSIONS:

Core Classification: CORE Supplementary.

$LC_{50}$ (4-hour): >5.18 mg/L. However, since only 20% of the aerosol was respirable, the actual dose was less and the limit test was not achieved.

Toxicity Category: Not categorized.

8. SUMMARY:

A group of five Alpk:APfSD (Wistar-derived) albino rats/sex (Alderly Park, Cheshire, UK), approximately 7 weeks of age, were exposed nose-only to the test material at a concentration of 5.18 mg/L for 4 hours and observed for 14 days after exposure. A control group of five rats/sex was exposed to air only under similar conditions. Body weight was measured prior to exposure and on study days 2, 3, 8, and 15. Initial body weights ranged from 203 to 223 g for males and from 195 to 212 g for females. Rats were observed frequently during the exposure for overt signs of toxicity and subjected to a detailed clinical examination daily during the study. At study termination, rats were killed and subjected to a gross necropsy. Lungs with trachea attached and liver were weighed and fixed, along with any gross lesions, for possible histopathological examination (lungs were inflated with fixative).

The animals were exposed nose-only in restraining tubes (Battelle, Geneva, Switzerland), which were inserted into a 9.2 L double baffled perspex exposure chamber (ICI). The test material was pumped into a concentric-jet glass atomizer using a Gilson peristaltic pump. Dry, filtered air flowed through the atomizer at a rate of 10 L/min (KDG Flowmeters, Burgess Hill, Sussex, UK). Particulate concentration sampled close to the animals breathing zone was measured approximately every 30 minutes during the exposure using weighed 25 mm-diameter Vinyl Metrical (VM-1) filters (Gelman Sciences Ltd., Northhampton, UK). Concentration was determined gravimetrically by weighing the filters; concentrations were then verified using liquid chromatography. Particle size was measured using a Marple Cascade Impactor (Shaeffer Instruments Ltd., Oxon, UK), and the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated.

The MMAD ± GSD were 4.56 ± 2.06 μm. Approximately 20% of the particles (by weight) were <2.5 μm in diameter. Mean gravimetric and analytical concentrations were 6.2 ± 1.14 and 5.18 mg/L ± 0.093, respectively; analytical concentrations ranged from 2.65 to 6.3 mg/L. During the exposure, chamber temperature ranged between 19.0 and 19.9°C and in the test

group, humidity was between 54 and 56%. Compound-related clinical signs observed during the exposure included salivation, reduced response to sound, and slow, deep breathing. Immediately after the exposure, salivation, splayed gait, head and paw flicking, tail erection, subdued behavior, and shaking were observed in test animals, but not in controls. These effects generally subsided by day 2, were exhibited to a greater extent in females, and were considered by the study author to be an effect on the central and autonomic nervous system. During the observation period, only staining of the fur, ungroomed appearance, and piloerection persisted beyond day 2; piloerection persisted longer in test animals than controls, and staining was probably residual test material. In addition, two test males exhibited abnormal respiratory noise, which was attributed to irritation of the upper respiratory tract by the test material. Hunched posture, piloerection, stains around the nose, chromodacryorrhea, and wet fur were observed in both control and test animals immediately after the exposure; the study author attributed these findings to the forced restraint during the exposure. Body weight losses were significantly ($p < 0.05$-$0.01$) greater in test animals compared with those of controls during the first 2 days after exposure. Thereafter, weight gains were similar between control and test animals. Relative (to body weight) lung weight was significantly ($p < 0.05$) higher for test males than control males. This was attributed to pulmonary irritation. No animals died during the study, and no abnormalities were found at necropsy.

SHEET INGREDIENT INFORMATION IS NOT INCLUDED

9. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

The conduct and reporting of this study were adequate, and the reported data supported the study author's conclusions. No deaths were observed in this study, and therefore, the $LC_{50}$ was greater than 5 mg/L. The test material was only 57.6% pure, however, over [redacted]
Therefore, the gravimetric and chromatographic analysis measured the active ingredient, except for 1% other impurities, which were considered negligible. However, based on 2.5 µM being of respirable size, 20% of the dose was respirable and therefore, testing at higher concentrations is required to meet the limit according to EPA Pesticide Assessment guidelines (1984) for acute inhalation toxicity. Therefore, this study provided Supplementary data only.

The results of this study suggest that the test material may be neurotoxic, based on the clinical signs observed immediately after exposure, which included tail erection, head and paw flicking, and splayed gait.

A signed Quality Assurance Statement, dated August 25, 1988, was provided.

10. CBI APPENDIX: Appendix, Materials and Methods, CBI pp. 2-8.

# APPENDIX

Materials and Methods
(CBI pp. 2-8)

Sulfonate Reviews

Page _____ is not included in this copy.

Pages 36 through 42 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Nguyen B. Thoa, Ph. D 4/12/91
Section I , Toxicology Branch I
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Health Effects Division (H7509C) 4/12/91

DATA EVALUATION RECORD

STUDY TYPE: Subchronic feeding - rat (Guideline 82-1[a])

MRID NUMBER: 412099-02

TEST MATERIAL: Technical grade sulfosate (stated purity of 19.2% a. i. in water) (Batch No. EHC 0355-25).

SYNONYMNS: SC-0024 (formerly)

STUDY NUMBER(S): T-10888

SPONSOR: ICI Americas, Inc., Agricultural Products, Wilmington, DE.

TESTING FACILITY: Stauffer Chemical Co., Environmental Health Center, Farmington CN.

TITLE OF REPORT: 3-Month Dietary Toxicity Study with SC-0024 in Rats.

AUTHOR(S): Katz, A., and D. Frank

DATE REPORT ISSUED: April 3, 1987 (reformatted copy)

CONCLUSIONS: Based on an independent analysis of the results of the 3-month subchronic oral study, TB concludes that the NOELs were 800 ppm (36 mg/kg/day; MDT) in male rats and 2000 ppm (108 mg/kg/day; HDT) in female rats. The LOEL in male rats was 2000 ppm (88 mg/kg/day), based on a significant overall decrease of body weight gain (22% below control). At 2000 ppm, the females exhibited only some decrease in body weight which were significant but minimal and sporadic (6% at week 2, 8% at week 11, & 10% at week 13) and were concommitant with decreases in food consumption (21% at week 2, 18% at week 11, & 7% at week 13).

Food efficiency was independently calculated for each male or female rat from the control and HD groups. An overall body weight gain for each animal was determined by substracting its Day 0 weight from its Day 90 (for males) or Day 96 (for females) weight. Overall food consumption was determined for each individual animal by multiplying the daily food consumption reported for each observation period by the number of days in that period. These values were totaled for the 90- or 96-day duration of the study. Food efficiency was calculated by dividing the overall body weight gain by the total food consumption for each animal and multiplying the result by 100. The group mean $\pm$ standart deviation (SD) for food efficiency in each control and HD group were calculated for

males and females (20/sex/group), and a t test was performed to determine statistically significant differences.

The calculations showed that group mean ± standard deviation food efficiency for HD females (9.917± 1.905) was not statistically different from that of controls (10.28 ± 1.885; $p = 0.543$). Therefore, the observed sporadic decreases in body weight of the HD females were not due to a toxic effect of sulfosate but were secondary to a decrease in food consumption (Sulfosate is known to have a faint sulfur odor which may cause a palability problem especially in HD females since these consumed more test material than HD males).

On the other hand, group M ± SD food efficiency for HD males (18.74 ± 1.430) was statistically different from that of controls (21.13 ± 1.714; $p < 0.01$). This result indicates that the HD males' decreases in overall body weight gain were due to a toxic effect of sulfosate.

TB definitions of the LOELs are similar to the investigator's, but differ from the attached DER. The DER stated that the LOEL was 2000 ppm for both males and females. The basis for the LOEL in females was "sporadic depressions of body weight gain". Results reported in the study indicate that the overall decrease in females' body weight gain was not statistically significant and TB calculations clearly demonstrate that the sporadic decreases in body weight of females were secondary to a decrease in food consumption.

In addition, no significant changes were observed in any of the following: clinical observations, hematology, clinical chemistry, organ weights, and macroscopic/microscopic histopathology.

Core Classification: Minimum. The MTD was achieved only in male rats.

CONFIDENTIAL BY ... IS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

CASWELL FILE

EPA No.: 68D80056
DYNAMAC No.: 309-A
TASK No.: 3-09A
March 19, 1991

008348

# DATA EVALUATION RECORD

## SULFOSATE

## Subchronic Oral Toxicity Study in Rats

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: 3/15/91



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EPA No.: 68D80056
DYNAMAC No.: 309-A
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March 19, 1991

DATA EVALUATION RECORD

SULFOSATE

Subchronic Oral Toxicity Study in Rats

REVIEWED BY:

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Date: 4/12/91



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DATA EVALUATION RECORD

GUIDELINE §82-1

STUDY TYPE: Subchronic oral toxicity study in rats.

MRID NUMBER: 412099-02.

TEST MATERIAL: Sulfosate.

SYNONYMS: SC-0224; Trimethylsulfonium salt of N-(phosphonomethyl)glycine; carboxymethylaminomethyl phosphonate.

STUDY NUMBER: T-10888.

SPONSOR: ICI Americas Inc., Wilmington, DE.

TESTING FACILITY: Stauffer Chemical Company, Environmental Health Center, Farmington, CT.

TITLE OF REPORT: 3-Month Dietary Toxicity Study with SC-0224 in Rats.

AUTHORS: Katz, A, and Frank, D.

REPORT ISSUED: April 3, 1987 (Reformatted copy).



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CONCLUSIONS:

Sulfosate was fed to male and female Sprague-Dawley rats (20/sex/group) at dose levels of 0, 150, 350, 800, or 2000 ppm (0, 7, 16, 36, or 88 mg/kg/day, males; 0, 8, 20, 43 or 108 mg/kg/day, females) for 13 weeks. Body weight gains and food consumption of high-dose males were depressed consistently throughout the study; high-dose females exhibited sporadically depressed body weight gains. Compound consumption appeared to decrease during the duration of the study; males exhibited the greater change. There were no compound-related effects on mortality, clinical observations, hematology, clinical chemistry, organ weights, or gross or microscopic pathology. The LOEL is 2000 ppm, and the NOEL is 800 ppm sulfosate.

Classification: CORE Minimum: The methodology of diet analysis should be clarified by the study authors; results of analysis varied widely (see Reviewers' Discussion and Interpretation of Results).

A. MATERIALS:

1. Test Compound: Sulfosate; description: clear, aqueous solution; batch No.: EHC 0355-25; purity: 19.2% a.i. solution in water.

2. Test Animals: Species: rat; strain: Sprague-Dawley [CR Crl:CD(SD)Br]; age: 6 weeks at study initiation; weight: males--132 to 229 g, females--141 to 179 g at study initiation; source: Charles River Breeding Laboratories, Kingston, NY.

B. STUDY DESIGN:

1. Animal Assignment: Rats were ranked by body weight and assigned to the following test groups such that group mean body weights did not vary significantly at the time of assignment.

| Test group | Dose in diet[a] (ppm) | Main study (3 months) Males | Females |
|---|---|---|---|
| 1 Control | 0 | 20 | 20 |
| 2 Low (LDT) | 150 | 20 | 20 |
| 3 Mid A (MDT) | 350 | 20 | 20 |
| 4 Mid B (MDT) | 800 | 20 | 20 |
| 5 High (HDT) | 2000 | 20 | 20 |

[a]Doses represent actual concentrations of SC-0224 a.i. in the diet.



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Animals were housed individually in a room with temperature and humidity controls set at 19 to 24°C and 40 to 60%, respectively, with a 12-hour light/dark cycle.

2. Diet Preparation: Diets were prepared weekly and stored at 4°C until use. A concentrated premix of the diet was prepared by mixing the appropriate amount of test material directly with the rodent chow. The test diets were prepared by blending the premix with the appropriate amount of untreated diet to give the required concentrations. Untreated diet was provided for the control animals. Samples of the initial four test diet blends were analyzed for a.i. concentration; concentration analyses were performed monthly thereafter. Homogeneity was analyzed at one or two intervals during the study for the three highest doses, and stability was analyzed at 4°C and ambient temperature using 690- and 800-ppm test diets.

   Results: Concentration, homogeneity, and stability analyses were performed separately on anions and cations of sulfosate test diets; the methodology of analysis was not reported.

   The 350-ppm test diets were not considered to be homogeneous; coefficients of variation for nine samples of the anion and cation analyses were 14 and 15%, respectively. The 800- and 2000-ppm diets were considered to be homogeneous; coefficients of variation for nine analyzed samples of anions were 6 and 10% for two separate blends of the 800-ppm diets and 7% for the 2000-ppm diet. Coefficients of variation for the analyzed cations were 10 and 7% for the 800- and 2000-ppm diets, respectively. The 150-ppm diets were not analyzed.

   The test compound was stable in the diet for 14 to 15 days at 4°C and at ambient temperature; the anion concentration of the 800-ppm diet was 90% of nominal after 15 days at 4°C and room temperature, and the cation concentration of the diet was 93% of nominal at room temperature and 98% of nominal after 14 days at 4°C.

   The concentrations of test material in the diets were within 7% of nominal for analysis of the anion. The mean concentrations for four to six intervals of analyses were 161.3 ± 22.5, 335 ± 19.1, 761.7 ± 67.9, and 1960 ± 151.7 ppm sulfosate for the 150-, 350-, 800-, and 2000-ppm diets, respectively. The analyzed cation concentrations of test material in the diets were not within an acceptable range of deviation from nominal; the mean concentrations for four intervals of analysis were 105 ± 5.8, 272.5 ± 47.9, 680 ± 72.6, and 1725 ± 206.2 ppm sulfosate for the 150-, 350-, 800-, and 2000-ppm diets, respectively.

3. Food and Water Consumption: Animals received food (Purina purified rodent meal No. 5755 M) and water ad libitum.

4. Statistics: The following procedures were utilized in analyzing the numerical data: Body weights, food consumption, hematology, clinical chemistry, and organ weights were analyzed by analysis of variance and Dunnett's t-test.

5. Quality Assurance: A quality assurance statement was signed but not dated. Quality Assurance was conducted from July to October 1982.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected at least twice daily for general appearance, behavior, signs of morbidity and mortality. In addition, all test animals were given a general physical examination that included palpation for masses once per week.

   Results: No deaths occurred during the study. No palpable mass observations were reported. No behavioral changes were reported. Clinical findings (dehydration, emaciation, rough coat, chromorhinorrhea, chromodacryorrhea, and alopecia) were found sporadically in control and dosed males and females and were not considered to be related to dosing (Table 1). Somatomotor activity of the test animals was not monitored.

2. Body Weight: Rats were weighed at study initiation and weekly thereafter.

   Results: Representative data on mean body weights and body weight gains are summarized in Table 2. Body weight gains for the 13 weeks of the study were reduced by 22% and 11% in high-dose males and females, respectively, as compared to concurrent control weight gains; this depression was significant ($p < 0.01$) in males. Mean body weights of high-dose males were significantly ($p < 0.05$) reduced at study weeks 2 (10%), 4 (6%), 5 (7%), 6 (10%), and 8 through 13 (13% at week 13). Mean body weights of high-dose females were significantly ($p < 0.05$) reduced at study weeks 2 (6%), 11 (8%), and 13 (10%). Body weights and body weight gains of other dosed animals were similar to concurrent controls with the exception of a significantly ($p < 0.05$) depressed mean body weight of females fed 150 ppm at week 11. This depression may have been the result of lower individual body weights in four animals of this group as a result of dehydration.

TABLE 1. Incidences of Selected Clinical Findings in Rats Fed Sulfosate for 13 Weeks[a]

| | Dose Group (ppm) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | Females | | | | |
| Clinical Finding | 0 | 150 | 350 | 800 | 2000 | 0 | 150 | 350 | 800 | 2000 |
| Dehydration | 2(0)[b] | 4(21) | 5(7) | 0 | 1(28) | 2(21) | 4(28) | 3(28) | 3(28) | 2(21) |
| Emaciation | 0 | 3(21) | 0 | 0 | 1 (7) | 0 | 0 | 0 | 1(56) | 0 |
| Rough coat | 0 | 1(56) | 0 | 0 | 0 | 2(83) | 0 | 1(70) | 3(90) | 2(83) |
| Chromorhinorrhea | 7(0) | 4(7) | 4(0) | 3(0) | 2(0) | 3(21) | 0 | 0 | 0 | 1(21) |

[a]Based on 20 rats/sex/dose.

[b]First study day of observation.

TABLE 2. Representative Results of Mean Body Weights (± S.D.) and Mean Body Weight Gains of Rats Fed Sulfosate for 13 Weeks[a]

| Dose (ppm) | Mean Body Weight (g) at Week: 0 | 4 | 8 | Termination[b] | Mean Body Weight Gain (g)[c,d] Weeks 0 to 13 |
|---|---|---|---|---|---|
| | | | Males | | |
| 0 | 194 ± 24 | 362 ± 29 | 460 ± 41 | 546 ± 52 | 352 ± 45 |
| 150 | 199 ± 15 | 370 ± 21 | 456 ± 38 | 531 ± 32 | 333 ± 31 |
| 350 | 203 ± 11 | 365 ± 24 | 457 ± 31 | 528 ± 38 | 325 ± 35 |
| 800 | 201 ± 12 | 367 ± 22 | 466 ± 35 | 525 ± 46 | 325 ± 39 |
| 2000 | 201 ± 13 | 341 ± 30* | 427 ± 32* | 477 ± 43* | 276 ± 40** |
| | | | Females | | |
| 0 | 161 ± 9 | 230 ± 20 | 269 ± 26 | 302 ± 41 | 141 ± 35 |
| 150 | 160 ± 9 | 230 ± 22 | 265 ± 21 | 305 ± 29 | 145 ± 25 |
| 350 | 160 ± 8 | 228 ± 29 | 267 ± 25 | 314 ± 33 | 153 ± 30 |
| 800 | 162 ± 8 | 237 ± 20 | 272 ± 33 | 303 ± 29 | 141 ± 25 |
| 2000 | 162 ± 10 | 228 ± 12 | 259 ± 15 | 287 ± 24 | 125 ± 21 |

[a]Based on 20 rats/sex/dose.

[b]Study day 90 for males and study day 96 for females.

[c]Calculated by reviewers as group means of individual body weight gains.

[d]Statistically analyzed by the reviewers using analysis of variance.

*Significantly different from control value at $p < 0.05$.

**Significantly different from control value at $p < 0.01$.

3. Food Consumption and Compound Intake: Consumption was determined, and mean daily diet consumption was calculated weekly. Compound intake was calculated from the consumption and body weight gain data.

Results: Analysis of food consumption data was reported by the study authors to reveal no significant trends; however, sporadic significant differences in food consumption were seen in dosed animals throughout the study. The food consumption (g/animal/day) of high-dose males was slightly but significantly ($p < 0.05$) depressed at most weekly intervals for the 13 weeks of the study; this was considered by the reviewers to be related to dosing and body weight loss (depression of food consumption at study weeks 1, 2, 4, 5, and 8 to 13). The food consumption of all dosed males and females was significantly ($p < 0.05$) depressed at week 11; this was not considered by the reviewers to be compound related but due to a technical problem. Excessive food consumption was seen for certain animals in all groups on examination of the individual animal data. This was attributed to food spillage, and the values (marked with asterisks in the individual animal data of the study report, pages 97 to 104) were not included in calculating mean values.

Representative compound consumption data are presented in Table 3; values attributed to food spillage were not included in calculating compound intake. Compound consumption appeared to decrease during the duration of the study in dosed males and females but appeared to be higher in females when compared to males. Compound consumption was recalculated by the reviewers without outlying values. The mean compound intakes for 13 weeks of the study were 6.9, 16.1, 36.3, and 88.3 mg/kg/day for males and 8.3, 19.8, 42.9, and 108.3 mg/kg/day for females. The control diets were not found to contain the test compound.

4. Ophthalmological Examinations: Ophthalmology examinations were not performed.

TABLE 3. Representative Results of Mean Compound Consumption (± S.D.) in Rats Fed Sulfosate for 13 Weeks[a]

| Dose (ppm) | Mean Compound Consumption (mg/kg body weight/day) at Week: 1 | 4 | 8 | Termination[b] | Mean Compound Consumption Weeks 0 to 13 |
|---|---|---|---|---|---|
| | | | Males | | |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 150 | 9.2 ± 0.8 | 7.7 ± 1.2 | 6.6 ± 0.7[d] | 5.5 ± 0.6 | 6.9 |
| 350 | 20.3 ± 1.6[c] | 16.6 ± 2.5 | 14.0 ± 1.7 | 13.3 ± 2.1 | 16.1 |
| 800 | 46.2 ± 4.0 | 40.1 ± 5.2 | 36.8 ± 3.6 | 29.1 ± 3.8[e] | 36.3 |
| 2000 | 96.3 ± 24.4 | 93.6 ± 18.6 | 86.7 ± 7.8 | 61.9 ± 7.7 | 88.3 |
| | | | Females | | |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 150 | 10.7 ± 1.4 | 8.5 ± 2.1 | 7.7 ± 1.2 | 6.3 ± 1.1 | 8.3 |
| 350 | 25.6 ± 3.3 | 22.4 ± 4.7[f] | 18.9 ± 3.1 | 13.9 ± 1.8 | 19.8 |
| 800 | 58.8 ± 9.2 | 44.1 ± 11.0 | 46.1 ± 8.4[g] | 27.0 ± 3.7 | 42.9 |
| 2000 | 135.6 ± 20.8 | 121.2 ± 24.7 | 113.0 ± 21.9 | 82.0 ± 11.3 | 108.3 |

[a]Reviewers recalculated means and standard deviations of values; the superscripts shown below indicate the omission of the following outlier values:

| | Reported | Outliers |
|---|---|---|
| [c] | 19.5 ± 4.1 | 3.2 |
| [d] | 6.4 ± 1.3 | 1.9 |
| [e] | 27.7 ± 7.1 | 3.2 |
| [f] | 20.8 ± 6.7 | 8.6, 3.7 |
| [g] | 43.9 ± 12.4 | 6.3 |

[b]Study day 90 for males and study day 96 for females.

5. Hematology and Clinical Chemistry: Blood was collected from the orbital venous plexus of 10 male and 10 female non-assigned rats, prior to study initiation, for the establishment of baseline hematology and clinical chemistry data. Blood was also collected at 6 weeks, and at study termination from 10 animals/sex/dose. The CHECKED (X) parameters were examined:

a. Hematology:

| | | | |
|---|---|---|---|
| X | Hematocrit (HCT)† | X | Leukocyte differential count† |
| X | Hemoglobin (HGB)† | | Mean corpuscular HGB (MCH) |
| X | Leukocyte count (WBC)† | | Mean corpuscular HGB concentration (MCHC) |
| X | Erythrocyte count (RBC)† | | Mean corpuscular volume (MCV) |
| X | Platelet count† | | Coagulation:thromboplastin time (PT) |
| X | Reticulocyte count (RETIC)[a] | | |
| | Red cell morphology | | |

Results: In males total leukocyte counts were significantly ($p < 0.05$) decreased at 6 weeks in groups receiving 350, 800, and 2000 ppm; however, there was no effect on differential counts, and the mean leukocyte count of controls was considerably higher than the pretest value. No similar effect was found at study termination. Erythrocyte counts of high-dose males were slightly but significantly ($p < 0.05$) depressed at 6 and 13 weeks; however, all individual values were within the range of concurrent controls and no changes were seen for other erythrocyte parameters. No effects were seen on hematology parameters in females. Hematological changes were not considered to be a result of dosing.

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†Recommended by Subdivision F (October 1984) Guidelines for subchronic toxicity studies.

[a]Reticulocytes were measured if signs of anemia were observed.

b. Clinical Chemistry:

| | Electrolytes |
|---|---|
| X | Calcium† |
| X | Chloride† |
| | Magnesium |
| X | Phosphorus† |
| X | Potassium† |
| X | Sodium† |
| X | Osmolality |

| | Enzymes |
|---|---|
| X | Alkaline phosphatase (ALP) |
| X | Cholinesterase (plasma, erythrocyte, brain)[a] |
| | Creatine phosphokinase† |
| X | Lactic acid dehydrogenase |
| X | Serum alanine aminotransferase (SGPT)† |
| X | Serum aspartate aminotransferase (SGOT)† |
| X | Gamma glutamyltransferase (GGT) |

| | Other |
|---|---|
| X | Albumin† |
| | Albumin/globulin ratio |
| X | Blood creatinine† |
| X | Blood urea nitrogen† |
| X | Cholesterol |
| X | Globulins |
| X | Glucose† |
| X | Total bilirubin† |
| X | Direct bilirubin[b] |
| X | Total protein† |
| X | Triglycerides |

Results: There were no effects of biological importance on clinical chemistry parameters. Sporadic significant changes in several parameters (triglycerides, LDH, SGOT, erythrocyte cholinesterase, cholesterol), primarily at 6 weeks in dosed males, were not dose related and were not consistent at 6 and 13 weeks. In addition, a large variation in data was exhibited for individual animals, although for the most part the range of values was similar in dosed and control groups. Changes in LDH and SGOT were not considered to be of biological importance; all changes that were statistically significant were decreased values. Only increased values would be considered to be indicators of toxicological significance for these parameters. Changes in erythrocyte cholinesterase were increased values; slightly increased erythrocyte cholinesterase values are not considered to be of toxicological importance.

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[a]Brain cholinesterase was measured at study termination only.

[b]Direct bilirubin was measured only when total bilirubin exceeded 0.4 mg/dL.

†Recommended by Subdivision F (November 1984) Guidelines.

6. Urinalysis: Urine was collected from fasted animals at study initiation, at 6 weeks, and at study termination from 10 animals/sex/dose. The CHECKED (X) parameters were examined:

| | | | |
|---|---|---|---|
| X | Appearance and color | X | Glucose |
| | Volume | X | Ketones |
| X | Specific gravity and/or osmolality | X | Bilirubin |
| | | X | Blood |
| X | pH | | Nitrate |
| X | Sediment (microscopic) | X | Urobilinogen |
| X | Protein | | |

Results: There were no effects of biological importance on the urinalyses of dosed animals.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination, and the CHECKED (X) tissues were collected. In addition, the (XX) organs were weighed.

| | Digestive System | | Cardiovasc./Hemat. | | Neurologic |
|---|---|---|---|---|---|
| X | Tongue | X | Aorta† | XX | Brain |
| X | Salivary glands† | XX | Heart† | X | Peripheral nerve (sciatic nerve)† |
| X | Esophagus† | X | Bone marrow† | | |
| X | Stomach† | X | Lymph nodes† | X | Spinal cord (3 levels) |
| X | Duodenum† | XX | Spleen† | | |
| X | Jejunum† | XX | Thymus† | X | Pituitary† |
| X | Ileum† | | | X | Eyes (optic nerve)† |
| X | Cecum† | | | | |
| X | Colon† | | | | |
| | Rectum† | | Urogenital | | Glandular |
| XX | Liver† | XX | Kidneys† | XX | Adrenals† |
| | Gallbladder† | X | Urinary bladder† | | Lacrimal gland |
| X | Pancreas† | XX | Testes† | X | Mammary gland |
| | | X | Epididymides | X | Thyroids† |
| | | X | Prostate | X | Parathyroids† |
| | | | Seminal vesicle | X | Harderian glands |
| | Respiratory | XX | Ovaries | | |
| X | Trachea† | X | Uterus† | | |
| X | Lung† | | | | |
| | | | | | Other |
| | | | | X | Bone (sternum) |
| | | | | X | Skeletal muscle |
| | | | | X | Skin |
| | | | | X | All gross lesions and masses† |

†Recommended by Subdivision F (November 1984) Guidelines for subchronic toxicity studies.



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All tissues were examined histologically in control and high-dose animals. Only liver, kidneys, heart and gross lesions were examined in low- and mid-dose animals.

Results:

a. Organ Weights: Table 4 presents data for heart, liver, and thymus weights. Absolute heart and liver weights of high-dose males were found to be slightly but significantly ($p < 0.05$) decreased by 8 and 14%, respectively, while absolute thymus weights of low- and high-dose males were depressed by 22.8 and 25.4%, respectively, from concurrent controls. In addition, relative weights of brain, kidneys, and testes were slightly but significantly ($p < 0.05$) elevated in high-dose males; these changes were not dose related (Table 4). The reviewers consider these changes to be a result of the decreased body weights of high-dose males throughout the study. The organ weight changes are not considered to be related to dosing.

b. Gross Pathology: There were no macroscopic pathological changes that were considered to be compound related by the study authors.

c. Microscopic Pathology: Representative histological findings are presented in Table 5. There were no histological findings that were considered by the study authors to be related to dosing. The increased incidence of mineralization or renal microcalcinosis observed in control and dosed females and the increased incidence of lymphoid hyperplasia in many tissues (jejunum, ileum, cecum, and colon) of the digestive system of control and high-dose males and females were reported by the study authors to be a result of the purified diet. The incidence of biliary hyperplasia appeared to be increased in a dose related manner in dosed females; however, this change did not occur in a similar manner in dosed males and there were no associated blood chemistry changes in the animals. The incidence of other histological findings (not discussed by the study authors but noted in Table 5) were similar between control and dosed animals and were considered

TABLE 4 Mean Organ Weights (g) of Rats Fed Sulfosat for 13 Weeks

| Dietary Level (ppm) | Males | | Females | |
|---|---|---|---|---|
| | Absolute (g) | Relative (%) | Absolute (g) | Relative (%) |
| | | Heart | | |
| 0 | 1.56 ± 0.16 | 0.30 ± 0.03 | 1.05 ± 0.18 | 0.36 ± 0.08 |
| 150 | 1.54 ± 0.13 | 0.30 ± 0.04 | 0.99 ± 0.07 | 0.35 ± 0.03 |
| 350 | 1.52 ± 0.13 | 0.30 ± 0.03 | 1.02 ± 0.10 | 0.34 ± 0.03 |
| 800 | 1.52 ± 0.13 | 0.30 ± 0.03 | 0.99 ± 0.10 | 0.34 ± 0.04 |
| 2000 | 1.43 ± 0.20* | 0.31 ± 0.03 | 0.99 ± 0.10 | 0.37 ± 0.04 |
| | | Liver | | |
| 0 | 11.35 ± 1.33 | 2.16 ± 0.17 | 7.00 ± 0.90 | 2.40 ± 0.21 |
| 150 | 11.34 ± 1.01 | 2.19 ± 0.14 | 7.13 ± 0.77 | 2.48 ± 0.24 |
| 350 | 12.02 ± 1.35 | 2.33 ± 0.17* | 7.32 ± 1.11 | 2.43 ± 0.25 |
| 800 | 11.55 ± 1.41 | 2.27 ± 0.18 | 7.15 ± 0.93 | 2.47 ± 0.28 |
| 2000 | 9.75 ± 1.36* | 2.15 ± 0.14 | 6.86 ± 0.72 | 2.58 ± 0.25 |
| | | Thymus | | |
| 0 | 0.497 ± 0.109 | 0.09 ± 0.02 | 0.292 ± 0.078 | 0.100 ± 0.023 |
| 150 | 0.384 ± 0.083* | 0.07 ± 0.02* | 0.266 ± 0.062 | 0.092 ± 0.020 |
| 350 | 0.434 ± 0.080 | 0.09 ± 0.02 | 0.353 ± 0.092* | 0.117 ± 0.023 |
| 800 | 0.447 ± 0.079 | 0.09 ± 0.01 | 0.307 ± 0.075 | 0.105 ± 0.022 |
| 2000 | 0.371 ± 0.069* | 0.08 ± 0.02 | 0.312 ± 0.063 | 0.117 ± 0.023 |
| | | Brain | | |
| 0 | 2.09 ± 0.09 | 0.40 ± 0.04 | 1.96 ± 0.05 | 0.68 ± 0.08 |
| 150 | 2.01 ± 0.07 | 0.41 ± 0.03 | 1.92 ± 0.06 | 0.67 ± 0.07 |
| 350 | 2.10 ± 0.09 | 0.41 ± 0.04 | 1.96 ± 0.07 | 0.66 ± 0.08 |
| 800 | 2.10 ± 0.09 | 0.42 ± 0.04 | 1.93 ± 0.06 | 0.67 ± 0.07 |
| 2000 | 2.06 ± 0.07 | 0.46 ± 0.05* | 1.95 ± 0.07 | 0.74 ± 0.07 |
| | | Kidneys | | |
| 0 | 2.87 ± 0.35 | 0.55 ± 0.07 | 1.80 ± 0.19 | 0.62 ± 0.06 |
| 150 | 2.96 ± 0.29 | 0.57 ± 0.05 | 1.88 ± 0.18 | 0.66 ± 0.05 |
| 350 | 3.08 ± 0.29 | 0.60 ± 0.05 | 1.81 ± 0.23 | 0.60 ± 0.07 |
| 800 | 2.96 ± 0.27 | 0.58 ± 0.05 | 1.93 ± 0.30 | 0.67 ± 0.09 |
| 2000 | 2.86 ± 0.49 | 0.63 ± 0.11* | 1.78 ± 0.19 | 0.67 ± 0.08 |
| | | Testes | | |
| 0 | 3.38 ± 0.32 | 0.65 ± 0.08 | | |
| 150 | 3.54 ± 0.26 | 0.68 ± 0.04 | | |
| 350 | 3.34 ± 0.17 | 0.65 ± 0.07 | | |
| 800 | 3.42 ± 0.29 | 0.67 ± 0.08 | | |
| 2000 | 3.43 ± 0.36 | 0.76 ± 0.08* | | |

*Significantly different from control values at $p < 0.05$.

TABLE 5. Incidence of Nonneoplastic Lesions in Rats Fed SC-0224 for 13 Weeks

| Organ/Finding | Dietary Level (ppm) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | Females | | | | |
| | 0 | 150 | 350 | 800 | 2000 | 0 | 150 | 350 | 800 | 2000 |
| Mammary gland | (20) | (0) | (0) | (0) | (20) | (20) | (0) | (0) | (0) | (20) |
| Hyperplasia, mammary duct | 9 | 0 | 0 | 0 | 12 | 0 | 0 | 0 | 0 | 0 |
| Lung | (20) | (1) | (2) | (0) | (20) | (20) | (0) | (0) | (0) | (20) |
| Histiocytosis, pulmonary | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 |
| Mineralization, vascular | 11 | 0 | 2 | 0 | 12 | 4 | 0 | 0 | 0 | 7 |
| Vascular degradation/ hypertrophy | 4 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Atelectasis | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 3 |
| Heart | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) |
| Degradation, chronic myocardial | 10 | 7 | 7 | 3 | 5 | 0 | 0 | 1 | 1 | 2 |
| Thymus | (20) | (0) | (0) | (0) | (20) | (20) | (0) | (0) | (1) | (20) |
| Cyst, ultimobranchial | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Liver | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) |
| Hematopoiesis, extramedullary | 4 | 6 | 6 | 2 | 9 | 8 | 6 | 4 | 4 | 5 |
| Hyperplasia, biliary | 9 | 1 | 4 | 1 | 11 | 0 | 0 | 5 | 5 | 7 |
| Hepatitis, lymphocytic | 1 | 4 | 1 | 2 | 2 | 0 | 2 | 1 | 1 | 0 |
| Hepatitis, necrotic | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hepatitis, lympho-granulomatous | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 0 |
| Telangiectasia | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Capsulitis, chronic | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 1 |

(continued)

TABLE 5. (continued)

| | Dietary Level (ppm) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | Females | | | | |
| | 0 | 150 | 350 | 800 | 2000 | 0 | 150 | 350 | 800 | 2000 |
| Pancreas | (20) | (0) | (0) | (0) | (20) | (20) | (0) | (0) | (0) | (20) |
| Atrophy/degeneration, islet | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 |
| Kidney | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (20) |
| Mineralization | 1 | 1 | 0 | 0 | 1 | 18 | 19 | 20 | 19 | 19 |
| Hyperplasia, regenerative, tubular | 8 | 11 | 11 | 5 | 8 | 4 | 1 | 4 | 3 | 10 |
| Hydronephrosis | 4 | 2 | 1 | 1 | 3 | 2 | 4 | 2 | 1 | 2 |
| Pyelitis, lymphoid | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Nephritis, lymphocytic | 2 | 3 | 1 | 2 | 7 | 1 | 1 | 0 | 1 | 0 |
| Degeneration, tubular, hyaline droplet | 0 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Submaxillary salivary gland | (20) | (0) | (0) | (0) | (20) | (20) | (0) | (0) | (0) | (20) |
| Ectopic gland | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 |
| Prostate | (20) | (0) | (0) | (0) | (20) | | | | | |
| Prostatitis, lymphoid | 2 | 0 | 0 | 0 | 6 | | | | | |
| Epididymides | (20) | (0) | (0) | (0) | (20) | | | | | |
| Degeneration, vacuolar | 1 | 0 | 0 | 0 | 3 | | | | | |
| Uterus | | | | | | (20) | (2) | (0) | (0) | (20) |
| Hyperplasia, cystic, endometrial | | | | | | 0 | 0 | 0 | 0 | 3 |

(continued)

5. (continued)

| | Dietary Level (ppm) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | Females | | | | |
| | 0 | 150 | 350 | 800 | 2000 | 0 | 150 | 350 | 800 | 2000 |
| Thyroid/parathyroid | (20) | (20) | (20) | (20) | (20) | (20) | (20) | (19) | (20) | (20) |
| Cyst, squamous | 3 | 5 | 4 | 2 | 2 | 4 | 3 | 4 | 2 | 8 |
| Hyperplasia, intrafollicular | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Harderian gland | (20) | (0) | (0) | (0) | (20) | (20) | (0) | (0) | (0) | (20) |
| Hyperplasia, parathyroid | 2 | 0 | 0 | 1 | 2 | 0 | 2 | 0 | 0 | 0 |
| Dacryoadenitis, lymphocytic | 1 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 0 | 1 |

by the reviewers to be age- and strain-related changes. The incidence of findings in males appeared to be greater than that in females. However, the incidence of many of these findings in control and dosed animals appeared to be higher than that of comparative historical control animals[1] (e.g., extramedullary hematopoiesis of the liver, incidence of 20 and 45% in control and high-dose males and 40 and 25% in control and high-dose females compared to an incidence of 3 (6/200) and 10% (20/200) in historical male and female age- and strain-matched controls).

D. STUDY AUTHORS' CONCLUSIONS:

The 13-week dietary administration of sulfosate to male and female Sprague-Dawley rats at dose levels of 0, 150, 350, 800, or 2000 ppm resulted in reduced body weight gain in high-dose males. Females receiving this same dose exhibited minimal body weight depression. No other toxicologically significant changes were found in food consumption, clinical pathology, clinical observations, organ weights, gross pathology, or histology. The LOEL in male rats is 2000 ppm, and the NOEL is 800 ppm. The NOEL in female rats is 2000 ppm.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The study design was adequate, and the conduct of the study was acceptable. The methodology of dietary analysis (analyses conducted separately on anions and cations of sulfosate) should be clarified. There may be a problem with the analytical methodology of the study; however, this problem cannot be adequately evaluated with the data provided. In addition, homogeneity and stability analyses should have been conducted at all dose levels. The results of concentration and homogeneity analyses varied widely, and there appeared to be greater instability in the test diet at 15 days than at 28 days. Body weight gains were calculated by the reviewers. Since outlier values were prevalent for compound intake (outside those values attributed to food spillage), our reviewers recalculated selected data with and without outliers (Table 3). Opthalmoscopic examinations were not performed; in addition, clinical observations were incomplete.

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[1]Mobay Corporation. Nonneoplastic incidence report of control Sprague-Dawley rats.

Variation in data existed between individual animals for several clinical chemistry parameters. Many of these data were found to be statistically significant. However, the values were not dose related and were not consistent at 6 and 13 weeks, and the changes were not considered to be of biological significance. Some enzyme activity values (i.e., LDH, SGOT) were decreased when compared with mean control values; only increased values would be considered to be indicators of toxicological significance for these parameters. Erythrocyte cholinesterase activity was sporadically increased in dosed animals; slightly increased erythrocyte cholinesterase values are not considered to be of toxicological importance.

We agree with the study authors that the primary effect of sulfosate in rats of this study was a depression in body weight gain of high-dose males. However, the sporadic depression in body weight gain of high-dose females and depression of food consumption in high-dose males should also be considered. The LOEL is 2000 ppm, and the NOEL is 800 ppm sulfosate. The results and dose levels of this study may be used to determine dose levels used in a chronic oncogeneity study.



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CASWELL FILE

EPA No.: 68D80056
DYNAMAC No.: 309-B
TASK No.: 3-09B
March 15, 1991

008348

# DATA EVALUATION RECORD

## SULFOSATE

## 3-Month Oral Toxicity Study in Dogs

REVIEWED BY:

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Date: March 15, 1991

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DATA EVALUATION RECORD

GUIDELINE § 82-1

STUDY TYPE: Subchronic oral toxicity study in dogs.

MRID NUMBER: 412099-03.

TEST MATERIAL: SC-0224.

SYNONYMS: Sulfosate, touchtown, trimethylsulfonium, carboxy-methylaminomethyl phosphonate.

STUDY NUMBER: T-11002.

SPONSOR: ICI Americas, Inc., Wilmington, DE.

TESTING FACILITY: Stauffer Chemical Company, Farmington, CT.

TITLE OF REPORT: Three-Month Subchronic Oral Toxicity Study with SC-0224 in Beagle Dogs.

AUTHORS: Hastings, SE, and Zwicker, GM.

REPORT ISSUED: April 3, 1987.



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CONCLUSIONS:

When sulfosate was administered orally to groups of six male and six female beagle dogs for 12 weeks, no changes occurred in body weight, food consumption, urinalysis, organ weights, or macroscopic or microscopic pathology. Changes in hematology, cholinesterase activity, and other clinical chemistry findings were slight, inconsistent, and not considered to be of toxicological significance. Emesis and salivation occurred at greater frequency and earlier onset in high-dose males and females. The LOEL is 50 mg sulfosate/kg/day (HDT) and the NOEL is 10 mg sulfosate/kg/day (MDT).

Classification: CORE Minimum. Animals were considered to be unthrifty due to the occurrence of lung worms in control and dosed animals; no vaccination of dogs was reported.

A. MATERIALS:

1. Test Compound: SC-0224; description: clear aqueous solution; batch No.: EHC 0355-25; purity: 19.2% (w/w) active ingredient.

2. Test Animals: Species: dog; strain: beagle; age: 5 months at study initiation; weight: males--8.0 to 11.4 kg, females--6.5 to 10.1 kg; source: Hazleton Research Animals, Inc., Cumberland, VA.

B. STUDY DESIGN:

1. Animal Assignment: Following 5 weeks of acclimation and quarantine, animals were ranked by body weight and randomly assigned to the following test groups. Data on vaccinations were not provided.

| Test group | Dose level (mg/kg/day) | Main study (3 months) Males | Females |
|---|---|---|---|
| 1 Control | 0 | 6 | 6 |
| 2 Low (LDT) | 2 | 6 | 6 |
| 3 Mid (MDT) | 10 | 6 | 6 |
| 4 High (HDT) | 50 | 6 | 6 |



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2. Dose Preparation: Dosing solutions were prepared biweekly. Appropriate amounts of the test material were mixed with tapwater to prepare the desired concentrations. The dosing solutions were analyzed for concentration following the first three dose preparations and monthly thereafter. Homogeneity was determined once during the study. Stability of the test material in water was determined at ambient temperature and 4°C.

   Results: The analyzed dosing solution was found to be homogeneous and stable in water for up to 4 weeks at 4°C and ambient temperature. The analyzed dosing solution was also found to be stable for 1 week at 60°C; these samples were unavailable for testing after this time. The concentrations of the test material in the vehicle were within 5% of nominal concentrations.

3. Administration of Test Material: The test material was administered by gavage, 5 days/week for 3 months, at a dose volume of 0.5 mL/kg body weight. Administered volume was adjusted weekly based on most recent body weight. Controls were administered the water vehicle in the same manner as dosed animals.

4. Food and Water Consumption: Animals received food (Purina Certified Canine Diet No. 5007, 300 to 500 g/day) and water ad libitum.

5. Statistics: The following procedures were utilized in analyzing the numerical data: Means and standard deviations were calculated for body weight, food consumption, hematology, and clinical biochemistry data. Although the study authors indicated that appropriate statistical analyses were performed on hematology and clinical biochemistry data, identification of the specific analyses was not indicated.

6. Quality Assurance: A quality assurance statement was signed but not dated.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected at least twice daily for signs of morbidity and mortality. In addition, all dogs were given a general physical examination once per week. A detailed physical examination was performed monthly.



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Results: No deaths occurred during the study. Dosed animals exhibited transient emesis and salivation prior to or immediately following dosing (Table 1). These symptoms occurred with the greatest frequency and earlier onset in males and females dosed with 50 mg/kg.

2. Body Weight: Body weights were recorded at study initiation and weekly thereafter.

   Results: Representative data on mean body weights are summarized in Table 2. Body weights and body weight gains of dosed animals were similar to concurrent controls throughout the study. The body weights of high-dose males and females did not vary by more than 7% from controls at study week 13 even though emesis was prevalent in these animals.

3. Food Consumption and Compound Intake: Food consumption was determined, and mean daily diet consumption was calculated daily.

   Results: The food consumption of dosed males and females was similar to that of concurrent controls.

4. Ophthalmology: Ophthalmological examinations were performed prior to study initiation and at study termination.

   Results: One low-dose male exhibited conjunctivitis in both eyes and a prolapsed gland of the eyelid at study termination; the right eye of this animal was reported to be red and swollen at study initiation. The conjunctiva of the right eye of one mid-dose female was reported to be red at study initiation; this condition cleared prior to study termination. These findings were not considered related to dosing.

5. Hematology and Clinical Chemistry: Blood was collected from all dogs prior to study initiation, at 6 weeks, and at study termination for hematology and clinical analysis. The CHECKED (X) parameters were examined:

TABLE 1. Incidence of Selected Clinical Observations in Dogs Administered Sulfosate for 3 Months

| | Dose Group (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 2 | 10 | 50 | 0 | 2 | 10 | 50 |
| Emesis | 1(51)[a] | 2(74) | 3(60) | 6(29) | 4(49) | 0 | 3(50) | 6(14) |
| Salivation (transient) | 0 | 0 | 1(50) | 3 (8) | 0 | 0 | 0 | 5(7) |

[a]First study day of observation.



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TABLE 2. Representative Results[a] of Mean Body Weights (± S.D.) in Dogs Administered Sulfosate for 3 Months

| Dose (mg/kg/day) | Mean Body Weight (kg) at Study Week: 0 | 3 | 7 | 13 |
|---|---|---|---|---|
| | | Males | | |
| 0 | 9.9 ± 1.2 | 10.9 ± 1.4 | 11.2 ± 1.2 | 12.3 ± 1.4 |
| 2 | 9.2 ± 1.1 | 10.1 ± 1.2 | 10.7 ± 1.2 | 11.9 ± 1.0 |
| 10 | 9.5 ± 1.1 | 10.3 ± 1.4 | 10.5 ± 1.4 | 11.2 ± 1.7 |
| 50 | 9.5 ± 1.0 | 10.5 ± 1.3 | 10.8 ± 1.2 | 11.5 ± 1.3 |
| | | Females | | |
| 0 | 8.3 ± 1.0 | 9.1 ± 1.2 | 9.7 ± 1.3 | 10.4 ± 1.3 |
| 2 | 7.8 ± 0.8 | 8.4 ± 0.8 | 8.8 ± 0.7 | 9.2 ± 0.8 |
| 10 | 8.2 ± 0.6 | 8.8 ± 0.6 | 9.1 ± 0.9 | 9.6 ± 1.0 |
| 50 | 7.9 ± 0.6 | 8.7 ± 0.7 | 9.3 ± 0.8 | 9.7 ± 0.7 |

[a]Based on six dogs/sex/dose group.

a. Hematology:

| | | | |
|---|---|---|---|
| X | Hematocrit (HCT)† | X | Leukocyte differential count |
| X | Hemoglobin (HGB)† | | Mean corpuscular HGB (MCH) |
| X | Leukocyte count (WBC)† | | Mean corpuscular HGB concentration (MCHC) |
| X | Erythrocyte count (RBC)† | | Mean corpuscular volume (MCV) |
| X | Platelet count† | | Coagulation:thromboplastin time (PT) |
| X | Reticulocyte count (RETIC)[a] | | |
| | Red cell morphology | | |

Results: Red cell indices (erythrocyte count, hemoglobin and hematocrit concentration) were slightly depressed (3-5%) in low-dose males and slightly increased in mid-dose males (6%) at 6 weeks when compared to concurrent controls; the changes were significant ($p < 0.05$) for hematocrit only. Red cell indices remained slightly depressed (3-5%) in low-dose males at study termination. Reticulocyte counts were not measured. These slight changes are not considered to be of toxicological significance.

b. Clinical Chemistry:

| | Electrolytes | | Other |
|---|---|---|---|
| X | Calcium† | X | Albumin† |
| X | Chloride† | | Albumin/globulin ratio |
| | Magnesium | X | Blood creatinine† |
| X | Phosphorus† | X | Blood urea nitrogen† |
| X | Potassium† | X | Cholesterol |
| X | Sodium† | X | Globulins |
| | | X | Glucose† |
| | Enzymes | X | Total bilirubin†, [b] |
| X | Alkaline phosphatase (ALP) | X | Direct bilirubin[b] |
| X | Cholinesterase (plasma, RBC, brain)[c] | X | Total protein† |
| | | | Triglycerides |
| | Creatine phosphokinase | | |
| X | Lactic acid dehydrogenase | | |
| X | Serum alanine aminotransferase (SGPT)† | | |
| X | Serum aspartate aminotransferase (SGOT)† | | |
| X | Gamma glutamyltransferase (GGT) | | |

[a]Reticulocytes were measured if the hematocrit of dosed animals was less than 35% of that of control animals.

[b]Direct bilirubin was measured if the total bilirubin was less than 0.4 mg/dL.

[c]Brain cholinesterase activity was measured in all animals sacrificed at termination.

†Recommended by Subdivision F (November 1984) Guidelines for Subchronic Studies.



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Results: Representative cholinesterase activity levels are presented in Table 3. Pretest plasma and erythrocyte cholinesterase activity levels were measured in one group of 26 males and 27 females before animals were divided into specific dose groups; these values are tabulated under control animals. Sulfosate did not affect the cholinesterase (plasma, erythrocyte, or brain) activity levels of beagle dogs. There was a significant ($p < 0.05$) increase in the level of red cell cholinesterase activity in high-dose males at 6 weeks and in the level of brain cholinesterase activity of low-dose males at 12 weeks. However, these increases were considered to be incidental and of no toxicological significance.

The authors reported several statistically significant changes in other clinical chemistry parameters between control and dosed groups; however, the changes were small, were not dose related, and were within the range of historical reference controls.[1] The reviewers do not consider these changes to be compound related. Table 4 presents data for GGT, albumin, and glucose. In addition, the levels of many electrolytes (sodium, calcium, chloride, phosphorus, potassium) were slightly changed at 6 or 12 weeks in dosed animals when compared with controls; however, these changes were sporadic and were within the range of historical reference controls.

6. Urinalysis and Fecal Examinations: Urine and fecal samples were collected from fasted animals prior to study initiation, at 6 weeks, and at study termination. The CHECKED (X) parameters were examined:

| | | | |
|---|---|---|---|
| X | Appearance | X | Glucose |
| | Volume | X | Ketones |
| X | Specific gravity | X | Bilirubin |
| X | pH | X | Blood |
| X | Sediment (microscopic) | | Nitrate |
| X | Protein | X | Urobilinogen |

Fecal samples were examined for occult blood and parasites.

[1] International Research and Development Corporation, Control Biochemical values.



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TABLE 3. Mean Cholinesterase Activity Levels (± S.D.) in Dogs Administered Sulfosate for 3 Months[a]

| | Dose (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| Parameter/Week | 0 | 2 | 10 | 50 | 0 | 2 | 10 | 50 |
| **Plasma Cholinesterase (U/L)** | | | | | | | | |
| 0 | 2157 ± 327 | | | | 2103 ± 348 | | | |
| 6 | 2032 ± 277 | 1806 ± 247 (89)[b] | 2087 ± 372(103) | 1829 ± 221(90) | 1970 ± 177 | 1933 ± 184(98) | 1864 ± 267(95) | 1972 ± 322 (100) |
| 12 | 1978 ± 263 | 1904 ± 286 (96) | 1878 ± 325 (95) | 1804 ± 165(91) | 1955 ± 227 | 2010 ± 165(103) | 1835 ± 212(94) | 1864 ± 350 (95) |
| **Red Blood Cell Cholinesterase (U/L packed RBC)** | | | | | | | | |
| 0 | 7363 ± 986 | | | | 7388 ± 665 | | | |
| 6 | 8267 ± 1303 | 8753 ± 271(106) | 9247 ± 1245(112) | 9950 ± 358*(120) | 9620 ± 227 | 9760 ± 283(101) | 8863 ± 1204(92) | 8733 ± 586(91) |
| 12 | 8493 ± 1376 | 6873 ± 1293 (81) | 8430 ± 1162 (99) | 8140 ± 838(96) | 8216 ± 1252 | 7510 ± 1108(91) | 6623 ± 705(81) | 7673 ± 1318(93) |
| **Brain Cholinesterase (U/g protein)** | | | | | | | | |
| 12 | 48.0 ± 5.9 | 58.0 ± 7.8*(121) | 43.5 ± 4.0(91) | 51.2 ± 7.8(107) | 49.1 ± 5.7 | 50.6 ± 11.5(103) | 47.9 ± 8.9(98) | 56.5 ± 8.6(115) |

[a]Based on six dogs/sex/dose with the exception of the pretest activity.

[b]Percent of control activity.

*Significantly different from controls at $p < 0.05$.

Table 4. Selected Clinical Chemistry Results (Mean ± S.D.) in Dogs Administered Sulfosate for 3 Months[a]

| Parameter/Week | Dose (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 2 | 10 | 50 | 0 | 2 | 10 | 50 |
| Gamma Glutamyl Transferase (GGT) (U/L) | | | | | | | | |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 | 1 ± 1 | 2 ± 1* |
| 12 | 2 ± 1 | 1 ± 1 | 2 ± 1 | 2 ± 1 | 1 ± 1 | 1 ± 1 | 1 ± 1 | 1 ± 1 |
| Albumin (g/dL) | | | | | | | | |
| 6 | 3.0 ± 0.1 | 3.0 ± 0.1 | 3.2 ± 0.1 | 3.1 ± 0.1 | 3.0 ± 0.1 | 3.1 ± 0.1 | 3.1 ± 0.2 | 3.4 ± 0.3* |
| 12 | 3.1 ± 0.1 | 3.2 ± 0.1 | 3.2 ± 0.2 | 3.2 ± 0.2 | 3.0 ± 0.1 | 3.3 ± 0.3 | 3.1 ± 0.1 | 3.3 ± 0.1 |
| Glucose (mg/dL) | | | | | | | | |
| 6 | 104 ± 5 | 110 ± 10 | 121 ± 3* | 123 ± 6* | 88 ± 4 | 98 ± 9 | 94 ± 5 | 93 ± 8 |
| 12 | 107 ± 7 | 115 ± 5 | 115 ± 3 | 104 ± 7 | 110 ± 9 | 109 ± 9 | 112 ± 7 | 112 ± 4 |

[a]Based on six dogs/sex/dose.

*Significantly different from controls at $p < 0.05$.

Results: There were no compound-related changes in urinalysis parameters. Isospora cysts were found in the feces of two males and six females prior to study initiation only; occult blood (trace to 2+) was found in the feces of two males and one female prior to study initiation and four males and four females at study termination.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathological examination, and the CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

| | | |
|---|---|---|
| Digestive System | Cardiovasc./Hemat. | Neurologic |
| Tongue | X Aorta† | XX Brain |
| X Salivary glands† | XX Heart† | X Peripheral nerve (sciatic nerve)† |
| X Esophagus† | X Bone marrow† | X Spinal cord (thoracic and lumbar) |
| X Stomach† | X Lymph nodes† | XX Pituitary† |
| X Duodenum† | X Spleen† | X Eyes (optic nerve)† |
| X Jejunum† | X Thymus† | |
| X Ileum† | | |
| X Cecum† | | |
| X Colon† | | |
| Rectum† | Urogenital | Glandular |
| XX Liver† | XX Kidneys† | X Adrenals† |
| X Gallbladder† | X Urinary bladder† | Lacrimal gland |
| X Pancreas† | XX Testes† | X Mammary gland† (with inginal skin) |
| | Epididymides | X Thyroids† |
| | XX Prostate | X Parathyroids† |
| Respiratory | Seminal vesicle | Harderian glands |
| X Trachea† | XX Ovaries | |
| X Lung† | X Uterus | |
| X Nasal cavity including turbinates | X Vagina and cervix | Other |
| | | X Bone (femur) |
| | | X Skeletal muscle |
| | | X Skin |
| | | X All gross lesions and masses† |

†Recommended by Subdivision F (November 1984) Guidelines for Subchronic Studies.

Results:

a. Organ weights: No toxicologically important changes in any organ weights were apparent. The slight variation of mean absolute and relative weights between groups was as normally expected.

b. Gross pathology: No gross findings were considered related to dosing. Pigmented focal areas of the lungs (reported by the study authors to be focal disseminated pneumonia and confirmed microscopically as lung worm infestation) were observed in dosed and control males and females (Table 5, lung data were combined for table). In addition, a nodule was found within the ear skin of one low-dose female. Other findings were considered to be normal age- and strain-related changes.

c. Microscopic pathology: Table 6 presents representative histologic findings. Histologic findings were not considered to be related to dosing with sulfosate. Lesions of the lungs (pneumonia, nematodiasis, hemorrhage) of dosed and control animals were reported to be the result of lung infestation of filarial nematodes. The ear skin nodule found macroscopically was diagnosed by the study authors as canine cutaneous histiocytoma and was considered to represent an inflammatory response of unknown etiology that often regresses spontaneously. Two minor bilateral tumors of the thyroid (papillary cystadenoma) of one low-dose male were cystic in appearance and were not considered to be compound related. Other microscopic lesions were reported to be inflammatory and of parasitic etiology.

D. STUDY AUTHORS' CONCLUSIONS:

The 12-week oral administration of sulfosate to male and female beagle dogs at dose levels of 0, 2, 10, or 50 mg/kg/day resulted in no significant effects at the low- and mid-dose level and produced only transient emesis and salivation at the high dose. The LOEL is 50 mg/kg/day, and the NOEL is 10 mg/kg/day.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The study design was adequate, and the conduct of the study was acceptable. However, data on vaccinations were not provided and microscopic evidence suggested that the dogs were infested with filarial nematodes. The authors reported, however, that



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TABLE 5. Representative Macroscopic Findings in Dogs Administered Sulfosate for 3 Months

| | Dose Group (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| Parameter | 0 | 2 | 10 | 50 | 0 | 2 | 10 | 50 |
| Brain | (6)[a] | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| Lateral ventricle dilation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Stomach | (6) | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| White/gray nodules | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 2 |
| Vagina | | | | | | | (1) | (1) |
| Enlarged/swollen | | | | | 0 | 0 | 1 | 1 |
| Lung | (6) | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| Pigmented focus | 4 | 0 | 2 | 4 | 2 | 3 | 6 | 3 |
| Nodule | 0 | 0 | 1 | 0 | 4 | 2 | 0 | 2 |
| Red streaks/ striations | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |

[a]Number in parentheses equals number of dogs examined.

TABLE 6. Representative Histopathological Findings in Dogs Administered Sulfosate for 3 Months

| Parameter | Dose Group (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 2 | 10 | 50 | 0 | 2 | 10 | 50 |
| Lung | (6)[a] | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| Interstitial pneumonia | 4 | 1 | 4 | 2 | 5 | 5 | 5 | 3 |
| Parasitic/eosinophilic granulomatous pneumonia | 2 | 0 | 1 | 1 | 3 | 3 | 1 | 1 |
| Nematodiasis | 3 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Hemorrhage | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Congestion | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Granuloma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Stomach | (6) | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| Lymphoid hyperplasia | 1 | 2 | 1 | 3 | 5 | 1 | 1 | 2 |
| Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Brain | (6) | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| Gliosis | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hydrocephalus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Liver | (6) | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| Microgranuloma | 1 | 4 | 3 | 3 | 5 | 1 | 3 | 2 |
| Granuloma | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Centrilobular periphlebitis | 1 | 2 | 0 | 0 | 3 | 2 | 3 | 1 |
| Thyroid | (6) | (6) | (6) | (6) | (6) | (6) | (6) | (6) |
| Intrafollicular microlithiasis | 2 | 1 | 1 | 2 | 1 | 2 | 1 | 3 |
| Papillary cystadenoma | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

[a]Number in parentheses equals number of dogs examined.

these lesions did not present any difficulty in evaluating tissues for compound-related changes. Pages 287 to 306 of the study report (study protocol) were not presented; data on vaccination procedures would have been included within these pages.

We agree with the study author's assessment that there were no apparent differences in body weight, food consumption, urinalysis, fecal analysis, organ weights, or macroscopic/microscopic pathology, and that the changes in hematology, cholinesterase activity levels and other clinical chemistry parameters were small, inconsistent, and devoid of toxicological significance. The only significant effect at the high dose was a greater frequency and earlier onset of emesis and salivation. For this reason, the reviewers propose that a higher dose level could have been tolerated by the dogs. The LOEL is 50 mg/kg, and the NOEL is 10 mg/kg.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

CASWELL FILE

EPA No.: 68D80056
DYNAMAC No.: 309-E
TASK No.: 3-09E
March 8, 1991

008368

# DATA EVALUATION RECORD

## SULFOSATE

## Metabolism in Rats

STUDY IDENTIFICATION: Boberg, E. W., and Ritter, J. C. ICIA-0224: Metabolism study in rats. (Unpublished Study No. T-12906 performed by ICI Americas, Inc., Farmington, CT; dated December 20, 1988.) MRID No. 412359-03.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: 3/6/91

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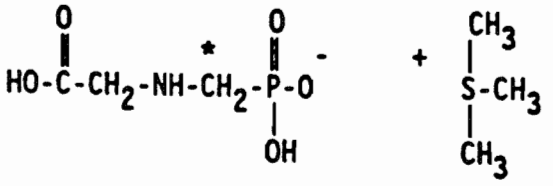
INERT INGREDIENT INFORMATION IS NOT INCLUDED

1. CHEMICAL: Sulfosate; ICIA-0224; trimethylsulfonium carboxymethylaminomethylphosphonate.

2. TEST MATERIAL: Unlabeled sulfosate (technical grade) and sulfosate labeled with $^{14}C$ at the methyl-phosphonate site were used. The unlabeled test material (lot No. WRC-8865-20-01) contained 56.2% active ingredient and [redacted] The specific activity and radiochemical purity of $^{14}C$-labeled sulfosate (lot No. WRC-8917-23-01) were 9.8 mCi/mmol and 93.2%, respectively. The structure and radiolabel position (*) of [$^{14}C$]sulfosate are shown below:



3. STUDY/ACTION TYPE: Metabolism in rats.

4. STUDY IDENTIFICATION: Boberg, E. W., and Ritter, J. C. ICIA-0224: Metabolism study in rats. (Unpublished Study No. T-12906 performed by ICI Americas, Inc., Farmington, CT; dated December 20, 1988.) MRID No. 412359-03.

5. REVIEWED BY:

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Date: 3-12-91

7. CONCLUSIONS:

A. [$^{14}$C]Sulfosate administered to rats was readily absorbed and rapidly eliminated. Approximately 90% of a single intravenous (iv) dose was excreted in the urine. Following administration of a single oral dose (25 or 250 mg/kg) or repeated oral doses (25 mg/kg), between 70 and 82% of the total radioactivity administered was eliminated within 24 hours and 85 to 94% within 120 hours. After administration of 25 mg/kg (single dose or repeated doses), 47 to 57% of the total radioactivity was excreted in the urine, and 36 to 42% was eliminated in the feces. The patterns of excretion were similar in both sexes. After administration of a single oral dose of 250 mg/kg, absorption was more saturated in females (54% of the radioactivity was eliminated in the feces; 36% was excreted in the urine) than in males (56 and 36% in the urine and feces, respectively). Biliary excretion was low, because only about 4% of an iv dose (25 mg/kg) was found in the feces.

Tissue $^{14}$C residue levels were low 5 days after dosing; all tissues combined (including liver, kidneys, brain, heart, spleen, skin, stomach and intestines plus contents, gonads, and blood) contained no more than 0.32% of the radioactive dose, and most $^{14}$C tissue concentrations (including those of high-dose rats) were ≤3 ppm. In contrast, carcasses contained up to 2.25% of the $^{14}$C dose, with most of the radioactivity found in the bone (2.7 to 7 ppm for low- and repeated-dose rats and 19.4 to 31.8 ppm for high-dose animals). These data suggest that [$^{14}$C]sulfosate may accumulate in the bones even after a single oral exposure. Repeated dosing did not affect the distribution of [$^{14}$C]sulfosate; $^{14}$C tissue levels in high-dose rats were proportionately higher than those in rats given a 25-mg/kg dose.

Most of the excreted radioactivity (77 to 96% of that in the feces, 80 to 90% of that in the urine) was recovered as unchanged anion (carboxymethylaminomethyl phosphonate). Several minor metabolites, each generally accounting for less than 3% of the excreted radioactivity, were also isolated. One compound recovered from the feces of repeated-dose females was tentatively identified as the decarboxylated metabolite aminomethylphosphonic acid. Other metabolites were not identified or characterized. Repeated oral exposure to sulfosate seemed to cause a slight increase in the production of some unidentified urinary metabolites.



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B. This study is acceptable and was conducted essentially according to EPA Guideline 85-1.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS:

A. Materials and Methods:

1. The radiopurity of [$^{14}$C]sulfosate (lot No. NRC-8917-23-0) was determined, according to the protocol supplied by the study authors (CBI p. 49), by either thin-layer chromatography (TLC) or high-performance liquid chromatography (HPLC) to be 93.2%. (The supplier, Stauffer Chemical Company, Richmond, CA, listed the material's radiopurity as 95.9%.) The detailed methodology used was not described in the materials and methods section of the report. The specific activity of the $^{14}$C-labeled sulfosate was 9.8 mCi/mmol. Unlabeled test material (lot No. C-8865-20-01) was 56.2% sulfosate and [redacted] no other components were listed. No additional details were provided.

2. Male and female Sprague-Dawley CRCrl:CD(SD)BR rats were purchased from Charles River Breeding Laboratories (Kingston, NY). The animals were 7 to 9 weeks old at the start of the study and weighed between 159 and 214 g (females) and 208 and 286 g (males). They were quarantined in steel cages for at least 7 days and then were acclimated in individual metabolism cages for 5 days. Animals were fasted for at least 8 hours before dosing.

3. Dosing solutions were prepared by mixing [$^{14}$C]sulfosate with unlabeled sulfosate and dissolving the mixture in distilled water. The $^{14}$C content of each dosing solution was determined by liquid scintillation counting (LSC). Solutions were administered using a dose volume of approximately 2.0 mL/kg; each animal received a total radioactive dose of 50 $\mu$Ci. The test material was stable in water at 4°C and at room temperature for 4 weeks (CBI p. 52). The unlabeled dosing solutions used in the 14-day repeated-dose study were prepared prior to study initiation and used throughout the dosing period. The doses used in this study were actual doses of the active ingredient.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

[1]Only items appropriate to this DER have been included.



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4. Groups of 10 rats (5/sex) were given, by gavage, either a single dose of 25 mg [$^{14}$C]sulfosate/kg (low-dose group), a single dose of 250 mg [$^{14}$C]sulfosate/kg (high-dose group), or a single dose of 25 mg unlabeled sulfosate/kg/day for 14 consecutive days followed by a single dose of 25 mg [$^{14}$C]sulfosate/kg on day 15 (repeated-dose group). An additional group of six rats/sex received a single iv dose (via the tail vein) of 25 mg [$^{14}$C]sulfosate/kg. Aliquots of the dosing solutions were analyzed by LSC, and the weights of the dosing syringes were taken before and after compound administration to determine the actual dose delivered.

   Urine and feces were collected separately over dry ice 6, 12, 24, 36, 72, 96, and 120 hours after dosing. Expired air was not collected since a pilot study indicated that only negligible amounts of [$^{14}$C]$CO_2$ were recovered in the air exhaled by rats given oral doses of [$^{14}$C]sulfosate (CBI pp. 13, 22). All animals were sacrificed 5 days after administration of the test material, and the following were collected for analysis: liver; kidneys; brain; small and large intestines plus contents; stomach plus contents; gonads; heart; spleen; lungs; samples of mesenteric fat, skeletal muscle, skin, and bone; and carcasses. The metabolic cages were rinsed with distilled water and a detergent and were wiped down to ensure maximal recovery of radioactivity The washes and wipes were collected for radioassaying.

5. Urine and plasma were analyzed directly for $^{14}$C content by LSC. Whole blood and red blood cells were solubilized and decolorized prior to analysis. Feces and gastrointestinal contents were homogenized in water, combusted, and analyzed for radioactive content. Tissue samples were homogenized when necessary, solubilized by incubation (in Soluene® 350), and counted. Carcasses were incubated overnight at 60°C in 15% KOH. The KOH-soluble portion was decanted and analyzed by LSC. Bone samples and KOH-insoluble portions of the carcass were incubated in 70% perchloric acid and 30% hydrogen peroxide at 70°C for 2 hours. Following this solubilization step, the samples were analyzed for $^{14}$C content. Appropriate measures were taken to determine counting efficiencies and to minimize color quenching.

6. Urinary and fecal sulfosate metabolites were characterized by TLC. Prior to spotting, the silica gel plates were sprayed until saturation with a solution of 0.25 M $K_2HPO_4$ and 0.25 M $K_3PO_4$ (pH 12.3), blotted dry, and stored. After spotting, the plates were developed with



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methanol:water (1:1, v/v). X-ray film was exposed to the TLC plates for visualization of metabolite spots. Radioactive areas were scraped off and assayed by LSC. Parent compound and one metabolite were characterized further by capillary gas chromatography/mass spectrometry (GC/MS).

Urine collected 0 to 72 hours after dosing was pooled by dose group. An aliquot of each pooled sample was filtered, evaporated to dryness, and redissolved in distilled water. Aliquots of the reconstituted urine were analyzed by TLC (as described above) and LSC. The major urinary metabolite was isolated from urine of high-dose rats and characterized further by TLC. Following chromatographic development, the radioactive band corresponding to this metabolite was scraped off the plate, mixed with acetic anhydride and anhydrous ethanol, and evaporated under nitrogen. The derivatized metabolite was then extracted with ethyl acetate and centrifuged; the supernatant was filtered, concentrated under nitrogen, and analyzed by capillary GC/MS. All feces samples were also pooled by dosing regimen prior to metabolite characterization. Portions of each pooled sample were extracted four times with distilled water; supernatants were combusted, filtered, and then concentrated by evaporation. TLC was performed on the concentrated extracts, and the distribution of $^{14}C$ on the plates was determined by autoradiography and LSC. The major fecal metabolite was isolated for spectral analysis, as described above.

7. Data were analyzed statistically using Duncan's multiple range test and a p level of 0.05 for detecting significant differences between groups.

B. Protocol: A protocol and protocol deviations for this study are presented in the Appendix.

12. REPORTED RESULTS:

A. Animals in the high-dose group received actual doses of 255 to 334 mg [$^{14}C$]sulfosate/kg (average ± S.D. = 299 ± 25 mg/kg). Rats in the low-dose groups received actual doses of 22.0 to 33.2 mg/kg (average ± S.D. = 26.4 ± 2.2 mg/kg).

B. Rats given the high dose were lethargic and dehydrated and had tremors, labored breathing, and excessive tearing for up to 72 hours after compound administration. Three high-dose rats (two males and one female) were severely affected and refused food. One male in the low-dose oral group lost hair from its left foreleg. All females and three of the

five males in the iv-dosed group exhibited orbital bleeding immediately after dosing; iv-dosed females also had labored breathing for about 1 minute postdosing. No other signs of toxicity were reported.

C. [$^{14}$C]Sulfosate was readily absorbed and eliminated by all animals. Within 24 hours after oral dosing, animals excreted 70.0 to 82.1% of the administered dose (31.8 to 51.8% in the urine and 23.9 to 38.2% in the feces). Within 24 hours of intravenous dosing, approximately 85 and 2% of the dose were recovered in the urine and feces, respectively. Twenty-four-hour average recoveries were not affected ($p < 0.05$) by sex or dosing regimen. Within 5 days after oral dosing, 87.5 to 96.9% of the $^{14}$C dose was recovered in the urine, feces, tissues, cage washes, and carcass (Table 1). The high-dose females excreted 36.1% of the administered oral dose in the urine and 53.5% in the feces. In contrast, the other groups excreted more radioactivity in the urine (50.8 to 57% of the administered dose) and less in the feces (35.6 to 42%). The differences between high-dose females and high-dose males or low-dose females were statistically significant ($p < 0.05$). Inter-animal variation in excretion of radioactivity was high, particularly among rats given the high dose. [Individual animal data are not presented in this DER; however, mean and standard deviation data for excretion of $^{14}$C can be found in Table 1.] For example, high-dose males excreted 36 to 82% and 9 to 56% of the $^{14}$C dose in the urine and feces, respectively, within 5 days; corresponding values for females were 20 to 54% and 33 to 71%. An increase in urinary excretion of $^{14}$C was associated with an increase in toxicity of the test material. Thus, the three high-dose animals that showed severe toxic signs excreted approximately twice as much of the $^{14}$C dose in the urine as did the other high-dose animals (i.e., 71 versus 36%, respectively; $p < 0.01$). In contrast, fecal levels of radioactivity were significantly lower ($p < 0.01$) in the severely affected high-dose rats (19%) than in the remaining seven animals (56%). The urine of iv-dosed rats of both sexes contained approximately 90% of the $^{14}$C dose at 5 days after dosing, whereas the feces accounted for 3 to 4%. All tissues combined contained less than 0.5% for all groups, and carcasses accounted for 0.60 to 1.04% (orally dosed rats) and 2.09 to 2.25% (iv-dosed rats). Cage washes of all animals represented about 0.3 to 1.5%.

D. Tissue $^{14}$C levels (ppm/wet weight) were low 5 days after dosing; all tissues combined accounted for ≤0.32% of the administered dose, and most tissues contained <1 ppm $^{14}$C (Table 2). An exception was the bone, which contained 2.7

TABLE 1. Mean Percent Recovery (± S.D.) of Radioactivity in Rats 5 Days After Oral or Intravenous Administration of [$^{14}$C]Sulfosate

| | Percent of [$^{14}$C] administered to rats dosed at: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 25 mg/kg (oral)[a] | | 250 mg/kg (oral)[a] | | 25 mg/kg (repeated oral)[b] | | 25 mg/kg (iv)[a] | |
| Fraction | Males | Females | Males | Females | Males | Females | Males | Females |
| Urine | 57.0 ± 9.7 | 50.8 ± 5.1 | 56.1 ± 21.7 | 36.1 ± 12.5 | 51.6 ± 7.4 | 47.3 ± 7.6 | 89.7 ± 2.3 | 89.6 ± 3.0 |
| Feces | 37.4 ± 11.4 | 38.2 ± 11.6 | 35.6 ± 22.1 | 53.5 ± 14.0 | 42.0 ± 6.6 | 37.8 ± 4.7 | 3.34 ± 1.3 | 3.93 ± 3.21 |
| Tissues[c] | 0.20 ± 0.02 | 0.29 ± 0.07 | 0.21 ± 0.07 | 0.31 ± 0.37 | 0.22 ± 0.05 | 0.23 ± 0.07 | 0.32 ± 0.06 | 0.32 ± 0.09 |
| Carcass[d] | 1.04 ± 0.19 | 1.00 ± 0.16 | 0.84 ± 0.32 | 0.60 ± 0.20 | 0.85 ± 0.15 | 0.91 ± 0.20 | 2.09 ± 0.10 | 2.25 ± 0.32 |
| Cage wash | 0.48 ± 0.30 | 1.41 ± 0.82 | 1.27 ± 1.06 | 0.78 ± 0.87 | 0.29 ± 0.13 | 1.20 ± 1.02 | 1.41 ± 1.32 | 0.39 ± 0.31 |
| Total | 96.2 ± 2.5 | 91.7 ± 8.8 | 94.0 ± 0.8 | 91.3 ± 2.7 | 95.0 ± 3.7 | 87.5 ± 7.8 | 96.9 ± 0.06 | 96.4 ± 1.7 |

[a]Animals (five or six/sex) were given a single oral or intravenous (iv) dose of [$^{14}$C]sulfosate.

[b]Animals (five/sex) were given a single oral dose of 25 mg unlabeled sulfosate/kg/day for 14 days followed by a single oral dose of 25 mg [$^{14}$C]sulfosate/kgon day 15.

[c]Includes total radioactivity in the liver, kidneys, brain, heart, spleen, total skin, small and large intestines, stomach, gonads, gastrointestinal contents, and whole blood.

[d]Includes KOH-soluble and insoluble carcass and separately analyzed femurs.

Source: CBI Tables 1 and 2, CBI pp. 23-25.

TABLE 2. Distribution of Radioactivity in Tissues of Rats 5 Days after Oral or Intravenous Administration of [$^{14}$C]Sulfosate

| | [$^{14}$C]Sulfosate equivalents (ppm) for rats dosed at: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 25 mg/kg (oral)[a] | | 250 mg/kg (oral)[a] | | 25 mg/kg (repeated oral)[b] | | 25 mg/kg (iv) | |
| Organ/Tissue | Males | Females | Males | Females | Males | Females | Males | Females |
| Liver | 0.309 ± 0.077[c] | 0.203 ± 0.047 | 2.260 ± 1.23 | 1.750 ± 0.640 | 0.225 ± 0.047 | 0.190 ± 0.040 | 0.367 ± 0.060 | 0.427 ± 0.123 |
| Kidneys | 0.311 ± 0.082 | 0.177 ± 0.042 | 2.750 ± 1.140 | 1.560 ± 0.700 | 0.251 ± 0.063 | 0.154 ± 0.034 | 0.530 ± 0.039 | 0.390 ± 0.048 |
| Brain | 0.091 ± 0.0282 | 0.0607 ± 0.0108 | 0.766 ± 0.330 | 0.508 ± 0.163 | 0.0755 ± 0.0195 | 0.0611 ± 0.0120 | 0.168 ± 0.015 | 0.151 ± 0.027 |
| Small intestine | 0.256 ± 0.070 | 0.457 ± 0.226 | 1.730 ± 0.806 | 3.120 ± 4.470 | 0.429 ± 0.154 | 0.402 ± 0.176 | 0.0970 ± 0.0222 | 0.112 ± 0.038 |
| Large intestine | 0.232 ± 0.141 | 0.246 ± 0.098 | 2.730 ± 0.930 | 7.380 ± 5.570 | 0.251 ± 0.060 | 0.322 ± 0.157 | 0.11 ± 0.033 | 0.117 ± 0.036 |
| Stomach | 0.110 ± 0.017 | 0.189 ± 0.079 | 1.680 ± 0.620 | 2.900 ± 0.832 | 0.136 ± 0.069 | 0.130 ± 0.0759 | 0.102 ± 0.022 | 0.106 ± 0.029 |
| Gonads | 0.042 ± 0.0114 | 0.0924 ± 0.0216 | 0.407 ± 0.215 | 0.940 ± 0.653 | 0.0405 ± 0.0081 | ND[d] | 0.0671 ± 0.0049 | 0.123 ± 0.047 |
| Heart | 0.0691 ± 0.0124 | 0.0445 ± 0.0043 | 0.614 ± 0.244 | 0.443 ± 0.096 | 0.0569 ± 0.0133 | 0.0407 ± 0.0098 | 0.131 ± 0.018 | 0.133 ± 0.047 |
| Spleen | 0.130 ± 0.0272 | 0.0908 ± 0.0174 | 1.060 ± 0.530 | 0.818 ± 0.201 | 0.106 ± 0.018 | 0.0982 ± 0.0208 | 1.160 ± 0.590 | 1.510 ± 0.500 |
| Lungs | 0.204 ± 0.037 | 0.145 ± 0.0306 | 1.370 ± 0.500 | 1.099 ± 0.351 | 0.152 ± 0.017 | 0.124 ± 0.034 | 0.421 ± 0.051 | 0.450 ± 0.091 |
| Fat | ND | ND | ND | ND | ND | ND | ND | ND |
| Muscle | ND | ND | ND | ND | ND | ND | 0.287 ± 0.380 | ND |
| Skin | 0.0714 ± 0.0220 | ND | 0.670 ± 0.390 | 0.779 ± 0.758 | ND | ND | 0.0760 ± 0.0288 | 0.0714 ± 0.0241 |
| Bone | 3.320 ± 0.530 | 2.900 ± 0.520* | 31.800 ± 14.300 | 19.400 ± 8.400* | 3.220 ± 0.500 | 2.680 ± 0.440 | 6.940 ± 0.699 | 4.610 ± 0.750 |
| Whole blood | 0.0373 ± 0.0077 | 0.0669 ± 0.0088 | 0.268 ± 0.108 | 0.173 ± 0.044 | 0.100 ± 0.042 | 0.0645 ± 0.0101 | 0.442 ± 0.148 | 0.443 ± 0.145 |

[a]Animals were given a single oral or intravenous (iv) dose of [$^{14}$C]sulfosate.

[b]Animals were given a single oral dose of 25 mg unlabeled sulfosate/kg/day for 14 days followed by a single oral dose of 25 mg [$^{14}$C]sulfosate/kg on day 15.

[c]Each value represents the mean (ppm wet weight) and standard deviation of five animals, except for values iv-dosed males, which represent the mean and standard deviation of six animals.

[d]Not detected.

*Significantly different ($p < 0.05$).

Source: CBI Tables 4 and 6, CBI pp. 30-31 and 34-35.

to 7 ppm for low-dose rats and 19.4 to 31.8 ppm for high-dose rats. The $^{14}C$ levels in liver, kidneys, lungs, and intestines of low- and repeated-dose animals were between 0.2 and 0.5 ppm. Similar to slightly higher $^{14}C$ concentrations were found in the spleen, liver, kidneys, lungs, and whole blood of iv-dosed animals. Tissue $^{14}C$ levels in high-dose rats were proportinately higher than those in low- and repeated-dose animals. Bone $^{14}C$ levels in high-dose females were significantly higher ($p < 0.05$) than those of low-dose female rats. Whole blood of both orally and intravenously dosed rats contained the lowest levels (<0.45 ppm). Analysis of data indicated no significant retention of $^{14}C$ in the tissues of repeated-dose rats.

E. Only one major area of radioactivity ($R_f$ 0.6) was seen on TLC plates spotted with urine or fecal extracts (extracts contained 64 to 89% of the total fecal radioactivity). This spot accounted for approximately 87 to 95.5% of the radioactivity in the urine and fecal extracts of single-dose rats (low and high), 77 to 84% of that excreted by repeated-dose rats, and 83 to 92% of that excreted by iv-dosed animals (Table 3). Several other faint spots were seen near the main area; however, these smaller spots generally accounted for less than 3% of the $^{14}C$ in the urine or in fecal extracts. One metabolite (2A), isolated from the feces of repeated-dose females, represented 8.50% of the extracted fecal $^{14}C$ of this group. The compound was tentatively identified as aminomethylphosphonic acid because its $R_f$ was similar to the $R_f$ of that standard in the same TLC system (CBI p. 21). Small amounts of radioactivity (0.30 to 2.70%) remained at the origin. Chromatographic and spectral analyses indicated that the major "metabolite" excreted by rats was unchanged parent compound. Other TLC spots were not characterized further, primarily because of insufficient material for analysis.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that low, high, and repeated oral doses of [$^{14}C$]sulfosate were readily absorbed and excreted by male and female rats. Within 5 days after compound administration, animals eliminated approximately 36 to 57 percent of the $^{14}C$ dose in the urine and 36 to 54 percent in the feces. The recovery of 90% of the $^{14}C$ in the urine of iv-dosed rats indicated that urinary levels of radioactivity approximated gastrointestinal absorption of [$^{14}C$]sulfosate, whereas fecal radioactivity represented the unabsorbed parent compound. Some sex- and dose-related



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TABLE 3. Distribution of Metabolites in the Urine and Feces of Rats Dosed Orally or Intravenously with [$^{14}$C]Sulfosate

| Radioactive Spot[c] | Percent of $^{14}$C excreted by rats dosed at: | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25 mg/kg (oral)[a] | | | | 250 mg/kg (oral)[a] | | | | 25 mg/kg (repeated dose)[b] | | | | 25 mg/kg (iv)[a] | |
| | Males | | Females | | Males | | Females | | Males | | Females | | Males | Females |
| | Urine | Feces | Urine | Feces | Urine | Feces | Urine | Feces | Urine | Feces | Urine | Feces | Urine[d] | Urine[d] |
| 1 (origin) | 0.75[e] | 2.00 | 0.32 | 0.51 | 0.47 | 1.06 | 0.57 | 0.82 | 0.30 | 1.52 | 0.30 | 2.70 | 0.53 | 0.48 |
| 2 | 0.58 | 1.16 | 0.96 | 1.61 | 0.11 | 2.44 | 0.68 | 1.10 | 1.87 | 7.35 | 1.66 | 2.66 | 0.92 | 1.88 |
| 2A | --[f] | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 8.50 | -- | -- |
| 3 | 0.63 | 94.83[g] | 0.74 | 95.52[g] | 0.26 | 92.83[g] | 0.58 | 95.26[g] | 1.15 | 84.25[g] | 0.97 | 77.10[g] | 1.58 | 2.34 |
| 4 | 1.55 | 2.01 | 4.03 | 2.27 | 2.09 | 3.66 | 2.13 | 2.82 | 3.59 | 6.87 | 3.87 | 9.04 | 2.19 | 2.98 |
| 5 | 94.65[g] | -- | 86.67[g] | -- | 94.64[g] | -- | 93.84[g] | -- | 82.76[g] | -- | 79.98[g] | -- | 91.73[g] | 82.67[g] |
| 6 | 1.77 | -- | 5.58 | -- | 2.22 | -- | 2.23 | -- | 7.03 | -- | 9.02 | -- | 2.17 | 6.25 |
| 7 | 0.06 | -- | 1.59 | -- | 0.19 | -- | 0.27 | -- | 2.80 | -- | 3.82 | -- | 0.76 | 2.74 |
| 8 | 0.02 | -- | 0.12 | -- | 0.02 | -- | 0.09 | -- | 0.52 | -- | 0.45 | -- | 0.13 | 0.68 |

[a]Animals were given a single oral or intraveneous (iv) dose of [$^{14}$C]sulfosate.

[b]Animals received a single oral dose of 25 mg unlabeled sulfosate/kg/day for 14 days followed by a single oral dose of 25 mg [$^{14}$C]sulfosate/kg on day 15.

[c]Metabolite numbers for urine and feces do not necessarily correspond to the same spot/metabolite.

[d]Fecal metabolites of iv-dosed rats were not quantitated.

[e]Values represent the mean of four samples.

[f]Not detected.

[g]Unchanged sulfosate.

Source: CBI Tables 7 and 9, CBI pp. 36 and 38.

unabsorbed parent compound. Some sex- and dose-related differences were observed in the excretion of $^{14}C$. For example, high-dose male rats eliminated a larger amount ($p < 0.05$) of radioactivity in the urine and a smaller amount ($p < 0.05$) in the feces than high-dose females. Similarly, high-dose female rats excreted more ($p < 0.05$) of the $^{14}C$ dose in the feces and less in the urine, when compared with low-dose females. In addition, there appeared to be a sex-independent relationship between the percent of the dose in the urine and the degree of toxicity observed: high-dose animals that had the most severe and prolonged toxic reaction to sulfosate eliminated 71% of the administered $^{14}C$ dose in the urine, whereas those least affected eliminated only 36% ($p < 0.01$). Thus, animals affected most severely absorbed more parent compound. The authors noted, however, that since food consumption decreased markedly in these animals, it was not possible to determine whether increased absorption was a cause or an effect of the toxicity. Repeated dosing had no effect on the route or rate of elimination of $^{14}C$ when compared with other groups.

Although $\leq 0.32\%$ of the $^{14}C$ dose was found in the tissues of all animals, 0.6 to 2.25% remained in the carcasses, mostly in the bones. The concentration of radioactivity in the bones of all dose groups is suggestive of bioaccumulation.

Unchanged parent compound accounted for approximately 80 to 95% of the total urinary radioactivity in all rats, 93 to 96% of that in fecal extracts of single-dose animals, and 77 and 84% of that in fecal extracts of repeated-dose males and females, respectively. These data indicated that sulfosate administered orally to rats remained mostly unmetabolized. A few minor metabolites were identifed; each of these generally accounted for less than 3% of the excreted radioactivity. A compound isolated only from the feces of repeated-dose females was tentatively identified as aminomethylphosphonic acid (AMPA). (AMPA is the principal degradation product of sulfosate in soil and is formed via microbial activity.) Representing 8.50% of the $^{14}C$ in fecal extracts of high-dose female rats, AMPA may have been formed by intestinal microflora in the gut.

B. A quality assurance/GLP compliance statement, signed and dated July 28, 1989, was included in the report.

14. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

This study was conducted adequately according to EPA guidelines (Pesticide Assessment Guidelines, Subdivision F, Hazard Evaluation Human and Domestic Animals, 1984, Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, pp. 152-156), and the authors' conclu-



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sions were supported by the data presented. Sufficient numbers of animals (five or six/sex/dose) were used, and the doses administered (low; high enough to produce signs of toxicity) and dosing regimens employed (single oral low and high, repeated low, and intravenous) were appropriate.

Orally administered [$^{14}$C]sulfosate was readily absorbed and eliminated by rats. Approximately 70 to 82 and 85 to 94% of the $^{14}$C dose were recovered from the urine and feces within 24 and 120 hours postdosing, respectively. Total recoveries (urine, feces, tissues, carcass, and cage washes) were between 87.5% and 96.9%; the value for repeated-dose females (i.e., 87.5%) was somewhat low, but all others were acceptable(≥ 90%). The recovery of 90% of the iv dose in the urine indicated, as the study authors suggested, that the $^{14}$C recovery values for the urine of orally dosed rats represented compound absorbed by the gastrointestinal tract; values for feces approximated the amount of unabsorbed sulfosate. Using fecal values, the reviewers calculated that, except for the high-dose females, all other dose groups absorbed about half of an oral dose of sulfosate. Absorption was significantly lower (<40% of an oral dose, $p < 0.05$) in high-dose females.

In general, tissue levels of radioactivity were low (<3 ppm; ≤0.32% of the $^{14}$C dose when combined) 5 days after dosing; in contrast, carcasses contained up to 2.25% of the $^{14}$C dose. Analysis of carcasses revealed that nearly all of this residual radioactivity was in the bones. As suggested by the study authors, these data suggested that sulfosate may accumulate in bone.

The reviewers agree with the study authors that sulfosate was not extensively metabolized by rats. However, repeated oral dosing may have caused a slight increase in the metabolism of the parent compound. Approximately 83 to 95.5% of the radioactivity excreted by animals given a single oral or intravenous dose of [$^{14}$C]sulfosate was parent compound; the corresponding values for repeated-dose rats were between 77 and 84% (Table 3 of this DER). An increase in the amount of certain metabolites excreted explained this shift. For example, metabolite 6 accounted for approximately 2 to 5.5% of the urinary radioactivity of single-dose animals but 7 to 9% of that of repeated-dose rats; similarly, urinary metabolite 7 represented 0.06 to 1.6 and 2.8 to 3.8%, respectively. In addition, approximately 7 to 9% of the fecal radioactivity of repeated-dose rats was metabolite 4, whereas this compound accounted for no more than 3.7% of that excreted by single-dose animals. The feces of repeated-dose males also contained a much larger amount of metabolite 2 than the feces of all other animals (i.e., 7.35% versus 0.92 to 2.44%, respectively). Finally, metabolite 2A, a fecal metabolite excreted by only repeated-dose females, accounted for 8.50% of the $^{14}$C in the feces.

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Although several of the metabolites listed in Table 3 of this DER represented 5 to 9% of the excreted radioactivity, none other than 2A was characterized further. Sketched TLC autoradiograms indicated that urinary metabolites 6 through 8 and fecal metabolite 4 were more polar than the parent compound. However, no additional information (i.e., $R_f$ values of standards versus unknown metabolites; results of additional chromatographic or spectral analyses) was provided for any metabolite other than 2A, which was tentatively identified as the decarboxylated metabolite aminomethylphosphonic acid (AMPA). The authors' suggestion that AMPA was formed by intestinal microflora seemed reasonable in light of the fact that the compound was found only in fecal samples and that AMPA is the principal microbial degradation product of sulfosate in soil.

The fate of the sulfonium ion was not investigated.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix, Protocol and Protocol Deviations, CBI pp. 46-67.

CASW

# APPENDIX

## Protocols and Protocol Deviations
## (CBI pp. 46-67)

CARPEL FILE

T-12906: SC-0224 METABOLISM STUDY IN RATS

## APPENDIX I

## STUDY PROTOCOL AND APPROVED PROTOCOL DEVIATIONS

Sulfosate Review

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Page _____ is not included in this copy.

Pages 98 through 119 are not included in this copy.

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The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

2 A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

√ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

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The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

008368

MAY 13 1991

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sulfosate - EPA File Symbols 10182-ETT and 10182-ETA (PP#9F3796) - Sulfosate in/on Corn - Touchdown 4LC and Touchdown Concentrate - Additional Toxicology Information and Partial Evaluation of Data

Caswell No.: 893C
Project No.: 0-0523
Record Nos.: 162448, 162449, 250410

FROM: William Dykstra, Reviewer *William Dykstra 5/10/90*
Review Section I
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Roger Gardner, Acting Section Head
Review Section I *Roger Gardner 5/12/90*
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

## Requested Action

Review submitted toxicology data in support of tolerance request for use of sulfosate in/on corn.

## Conclusions and Recommendations

1. The supplemental information to the 2-year combined chronic toxicity/oncogenicity studies in rats and mice are adequate to upgrade the core-supplementary status of those studies to core-guideline.

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2. The 1-year dog study can be upgraded to core-minimum data and supports the registration.

3. The following submitted studies have been sent to Dynamac for review:

| Study | Review Hours |
|---|---|
| 1. 21-Day Dermal Rat | 24 |
| 2. Acute Inhalation | 4 |
| 3. Metabolism (rat) | 24 |
| 4. 3-Month Dog | 120 |
| 5. 3-Month Rat | 120 |
| Total | 292 |

4. The company response to the review by Dr. Chen of the mouse micronucleus mutagenicity study has been transmitted to Dr. Chen for further comment.

5. Following resolution of items 2, 3, and 4, Toxicology Branch (TB) will evaluate the tolerance request for sulfosate in/on corn.

Review

I. TWO-YEAR COMBINED CHRONIC TOXICITY/ONCOGENICITY STUDIES IN RATS AND MICE

A. Supplemental Information

MRID Nos. 412099-07 and 412099-05; histopathology of individual animals with codes for individual animals.

1. T-11813; Addendum to Final Report of 2-Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Mice; prepared by ICI Americas.

2. T-11082; Addendum to Final Report of 2-Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Rats; prepared by ICI Americas.

3. Dictionary Codes for Histopathology Reports (hand carried on March 22, 1990 by Barbara Kaminski, ICI Americas) (attached).

B. Discussion

The January 5, 1988 review by W. Dykstra of the two 2-year chronic studies concluded the following:

"The 2-year rat feeding is considered a supplementary study. Evaluation of individual rat pathology sheets (Appendix N) did not provide a clear indication that tissue masses identified in the antemortem examination (Appendix I) and noted in the postmortem gross necropsy (Appendix L) were further evaluated microscopically. These deficiencies are required to be resolved." [End of quotation.]

"The 22-month mouse feeding study is considered a supplementary study. The tissue masses listed in Table I (clinical observations) and Table L (necropsy observations) were not clearly identified in the histopathology observations (Table N) as being histologically examined. This deficiency has to be resolved." [End of quotation.]

C. TR Conclusion

In the recent submission (MRID No. 412099-01), ICI stated that "in volumes 7 through 9, information will be submitted which we believe will greatly facilitate the tracking of tissue masses." [End of quotation.]

According to this submission:

"The following are being submitted for each study:

"1. Trail for individual clinical mass observations.

"2. Clarifications/annotations to trail.

"3. Necropsy detail report by animal with codes.

"4. Histopathology detail report by animal with codes.

"Necropsy and histopathology detail reports by animal were included in the original reports without codes. In the coded section to the extreme right of the enclose printouts, lesion numbers are listed which will clarify our tracking system. The Trail for Individual Clinical Mass Observation is an ancillary table prepared for EPA convenience." [End of quotation.]

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The only data received by TR at this time is item 4: Histopathological detail report by animal with codes for each study.

Additionally, the dictionary code, which was hand delivered, provides codes only for the individual histopathological findings for each animal in the addenda. A check between the original histopathological report and the newly submitted histopathological addendum, by using the dictionary code, shows that the original histopathological findings and the histopathological findings in the addenda are the same. Therefore, the coded information in the histopathological addenda can be verified.

However, items 1, 2, and 3 listed above of ICI's present submission are required to be submitted to complete the evaluation of tracking the tissue masses. In response to this situation, telephone communication on August 1, 1990 with Dr. Ann Manley, Toxicologist with ICI, provided the correct MRID Numbers for completing the evaluation of the 2-year rat and mouse studies. The MRID Numbers are 412099-05 (Rats) and 412099-07 (Mice). These MRID Numbers contained the individual animal data for tissue masses and gross necropsy findings for all rats on the study.

Analysis of randomly selected individual male and female rats and mice for tracking of tissue masses to gross necropsy findings to histopathological findings showed that the tracking of tissue masses could be correctly accomplished. This issue is considered resolved and the 2-year rat and 2-year mouse studies can be upgraded to core-guideline.

II. TWELVE-MONTH DOG STUDY

A. HED Review

Classification of Data: Supplementary

Deficiencies: The MTD was not employed for this study. The volume of urine for all animals at the treatment intervals was missing in this study report. Historical control data are needed to evaluate the incidence of abnormal protrusion of pituitary and the incidences of hamartoma and dermal histiocytoma of pinna described in this study.

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B. ICI Response to MTD Issue

"Dose level selection in dog studies.

"Stauffer Chemical Co. performed three toxicology studies on SC-0224 in dog.

"In the 28-day gavage study (ICI Reference Vol. 6), 8 doses of the technical grade active ingredient of 150 mg ai/kg gave rise to death within 3 days. The highest dose which proved to be sustainable over a 28-day period was 75 mg ai/kg/day. Emesis was evident at this dose in many of the animals dosed probably resulting in a lower dose being actually received.

"The 90-day study (ICI Reference Vol. 4) used a slightly lower top dose of 50 mg/kg, one third of the dose at which deaths had occurred in the preliminary study and two thirds of the dose producing emesis over 28 days. Emesis was again recorded at 50 mg ai/kg in the early part of this study along with increased salivation. There were no other treatment-related effects of toxicological significance in the study and a NOEL was established as the middle dose of 10 mg ai/kg/day.

"The gavage dose levels were employed in the one year study (EPA MRID No. 40214005), probably in the expectation of increased toxicity over the extended dosing period. In the event, no signs of toxicity including no emesis was observed in the study.

"While it cannot be argued that 50 mg ai/kg/day was a maximum tolerated dose in the one-year study based on evidence of toxicity in that study, 50 mg ai/kg/day did produce emesis in the 90-day study. Furthermore, 75 mg ai/kg/day produced significant and sustained toxicity over the 28-day period of the first study.

"50 mg ai/kg/day is therefore very close to the MTD in the one year study and 75 mg ai/kg/day would probably have not been sustainable over one year." [End of quotation.]

C. TB Conclusion Regarding the MTD

TB concurs with ICI that 50 mg/kg/day was appropriately selected based on preliminary findings and although the HDT did not produce chronic effects, TB concludes that the 1-year dog study is acceptable as core-minimum data on the basis of the MTD issue.

III. URINE VOLUME ABSENCE ISSUE

A. ICI Response

"Urine Volumes. Urine volumes were not measured in this study. Because of other normal findings in the study, there is no reason to believe that urine volumes would provide evidence for toxicity. Microscopic examination of kidneys showed no treatment-related changes in either sex. Normal background changes including presence of cysts, interstitial inflammation, mineralization and cytoplasmic vacuolization in proximal tubules were evident. Clinical laboratory parameters indicative of kidney function, including electrolyte levels, urinalyses, BUN and creatinine showed no consistent changes suggestive of a treatment effect." [End of quotation.]

B. TB Conclusion

TB concurs with the ICI explanation and concludes that the absence of urine volume measurement is of no toxicological significance in light of the available data.

IV. HISTORICAL CONTROL DATA ARE NEEDED TO EVALUATE THE INCIDENCES OF ABNORMAL PROTRUSION OF PITUITARY AND THE INCIDENCES OF HAMAPTOMA AND DERMAL HISTIOCYTOMA OF PINNA

A. ICI Response

"Historical Control Data for Microscopic Findings. In this study, the diagnosis of mucocele in the pituitary was used to describe cyst or cyst-like spaces containing an amorphous, basophilic to lightly eosinophilic, often whispy material suggestive of mucus. Mucoceles were universally located in the anterior pituitary (pars distalis) and occasionally extended to the hypophyseal (Rathkes') cleft. They were lined by flattened to cuboidal/columnar, pseudostratified, focally ciliated epithelium (see photographs #1 and 2). Analagous terms (used in other studies at the Environmental Health Center) include: cyst, cystic change, cystic dilatation of craniopharyngeal duct remnants, craniopharyngeal duct remnant, mucus cysts of craniopharyngeal duct and dilatation craniopharyngeal duct. Cysts of embryologic craniopharyngeal duct origin are frequently found in the dog pituitary gland. They have been reported to have incidences as high as 53% (Jones et al., 1983;

Jubb et al., 1985). Their presence and dose group distribution in this study is misleading and has no relationship to administration of SC-0224.

"The following is a tabular summary of historical control data from dog studies conducted at this facility:

"Historical Control Incidences of Pituitary Lesions Analagous to Mucocele in Beagle Dog Studies Conducted at Stauffer Chemical's - Environmental Health Center.

| Study | Duration | Pathologist | Lesion Name | Incidence Males | Incidence Females |
|---|---|---|---|---|---|
| T-11986 | 3 mo | Zwicker | cyst | 0/4[a] | 1/4 |
| T-11982 | 3 mo | Zwicker | cystic change (used when cysts multiple) | 1/4 | |
| | | | cyst | | 1/4 |
| T-11002 | 3 mo | Thomassen | cystic dilatation of cranio-pharyngeal duct remants | 0/6 | 0/6 |
| T-10125 | 3 mo | Thomassen | craniopharyngeal duct remnant | 1/6 | 0/6 |
| T-12625 | 1 yr | Taylor | mucus cyst craniopharyngeal duct (used when presence of mucus) | 1/5 | |
| | | | cyst pars distalis (used when no contents to cyst) | | 3/5 |
| | | | dilatation, cranio-pharyngeal duct (used when ciliated epithelium present and not distended enough to be diagnosed cyst) | | 1/5 |

[a]Numerator = # of animals with finding; denominator = # of animals in which pituitary gland was examined.

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| Study | Duration | Pathologist | Lesion Name | Incidence Males | Incidence Females |
|---|---|---|---|---|---|
| T-12723 | 1 yr | Taylor | cyst pars distalis | 0/5 | 2/5 |
| T-12969 | 6 mo | Zwicker | cystic change (used when cysts were multiple) | 0/4 | |
| | | | cyst | 0/4 | 3/4 |
| T-11872 | 3 mo | Turnier | cyst | 1/4 | 0/4 |

"Canine cutaneous histiocytoma (see photographs #3 and 4) is a benign, non metastasizing tumor unique to the dog. It is relatively common and occurs approximately 50% of the time in dogs under 2 years of age with no sex predisposition. The pinna is the most frequently site of involvement followed by the skin of the distal forelegs and forefeet. The majority of histiocytomas spontaneously regress (Moulton, 1978). At the Environmental Health Center we have encountered it only once before in a low dose female dog of another study. This mass was also present on the pinna. The presence of two histiocytomas (on the pinna) both of which were in the high dose (50 mg/kg/day) (1 male, 1 female) animals in T-11075 were chance observations unrelated to SC-0224 adminstration.

"Hamartoma is a <u>non-neoplastic</u> malformation composed of an abnormal mixture of tissue elements or an abnormal proportion of a single element that is normally present in that site. In this study the term hamartoma was used to describe the focal, nodular presence of an abnormal number of follicular and adnexal structures in the skin of the ear of a 2 mg/kg/day male dog (see photograph #5). The term has not been previously used in a dog study conducted at this laboratory." [End of quotation.]

"<u>References</u>

Tumors in Domestic Animals
Edited by Jack E. Moulton
University of California Press
Berkeley, Los Angeles, London 1978 pp. 24-26.
Endocrine System
Monographs on Pathology of Laboratory Animals sponsored by the International Life Sciences Institute
Edited by T.C. Jones, U. Mohr, P.D. Hunt

Springer - Verlag New York 1983 pp. 115-117, 161-163.
Pathology of Domestic Animals III ed Volume 3
K.V.F. Jubb, Peter C. Kennedy, and Nigel Palmer
Academic Press, Inc., New York 1985 pp. 244-245."
[End of quotation.]

B. TB Conclusions

TB concurs with ICI and concludes that the lesions of concern were not compound-related based on the available information.

Summary: The 1-year dog study can be upgraded to core-minimum status.

Note: The five photographs referred to in the ICI response to these pathology issues are not included with this memorandum.

V. DYNAMAC REVIEW

| | | Review Hours |
|---|---|---|
| A. | 21-Day Dermal Rat | 24 |
| B. | Acute Inhalation | 4 |
| C. | Metabolism (rat) | 24 |
| D. | 3-Month Dog | 120 |
| E. | 3-Month Rat | 120 |
| | Total Tech Hours | 292 |

The Dr. Chen review of the mouse micronucleus mutagenicity assay and the ICI Company response were sent to Dr. Chen on March 26, 1990 - 24 tech hours.

Attachment